

PATENT APPLICATION

SYNTHESIS OF 2-HYDROXY-N,N-DIMETHYL-3-[[2-[1(R)-(5-METHYL-2-FURANYL)PROPYL]AMINO]-3,4-DIOXO-1-CYCLOBUTEN-1-YL]AMINO]BENZAMIDE

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Synthesis of 2-Hydroxy-N,N-dimethyl-3-[[2-[1(R)-(5-methyl-2-furanyl)propyl]amino]-3,4-dioxo-1-cyclobuten-1-yl]amino]benzamide

Reference To Related Application

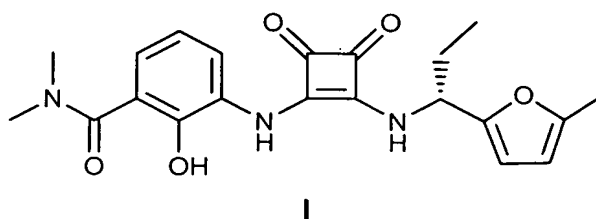
This application claims the benefit of U.S. Provisional Application Serial No. 60/463,773 filed April 18, 2003, the disclosure of which is incorporated herein by reference thereto.

Field of the Invention

This application discloses a novel process to synthesize 2-Hydroxy-N,N-dimethyl-3-[[2-[1(R)-(5-methyl-2-furanyl)propyl]amino]-3,4-dioxo-1-cyclobuten-1-yl]amino]benzamide.

Background of the Invention

2-Hydroxy-N,N-dimethyl-3-[[2-[1(R)-(5-methyl-2-furanyl)propyl]amino]-3,4-dioxo-1-cyclobuten-1-yl]amino]benzamide (compound of formula I):



is disclosed in U.S. Application Serial Nos. 10/122,841 (filed April 15, 2002 and now abandoned), 10/208,412 (filed July 30, 2002), and 10/241,326 (filed September 11, 2002), the disclosures of each being incorporated herein by reference thereto. The compound of formula I is also disclosed in WO 02/083624 (filed April 15, 2002 and published October 24, 2002).

The compound of formula I is useful for treating CXC chemokine-mediated diseases. Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T-cells, eosinophils, basophils, neutrophils and endothelial cells to sites of inflammation and tumor growth. The CXC-chemokines include interleukin-8 (IL-8), neutrophil-activating protein-1 (NAP-1), neutrophil-

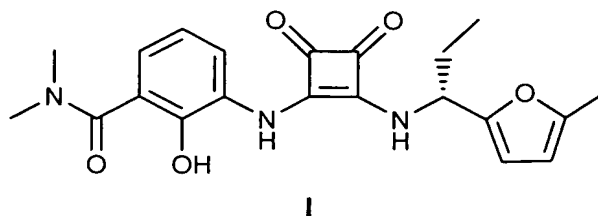
activating protein-2 (NAP-2), GRO α , GRO β , GRO γ , ENA-78, GCP-2, IP-10, MIG and PF4.

There remains a need for compounds that are capable of modulating activity at CXC-chemokine receptors. For example, conditions associated with an increase in IL-8 production (which is responsible for chemotaxis of neutrophil and T-cell subsets into the inflammatory site and growth of tumors) would benefit by compounds that are inhibitors of IL-8 receptor binding.

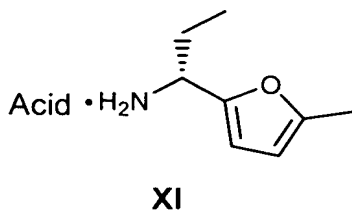
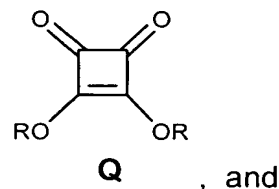
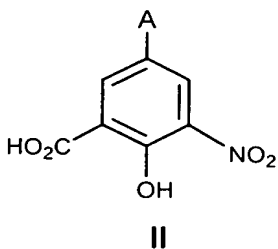
In view of the importance of antagonists that bind to the CXC-chemokine receptor novel methods of making such antagonists are always of interest.

Summary of the Invention

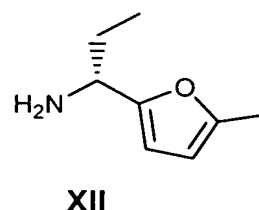
This invention is directed to a process for making the compound of formula I:



using the compounds of formulas II, Q, and XI or XII:

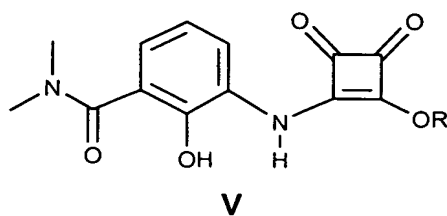


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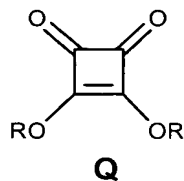
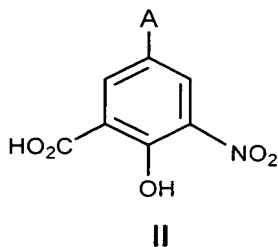


wherein A is selected from the group consisting of Br, Cl and I (with Br being preferred); and R represents (C₁-C₁₀)alkyl.

This invention is also directed to a process for making a compound of formula **V**:

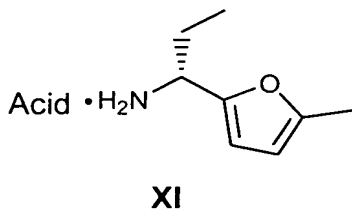


using compounds of the formulas **II** and **Q**:

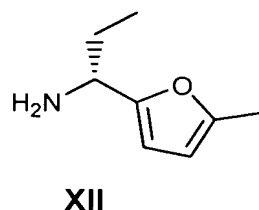


wherein A is selected from the group consisting of Br, Cl and I (with Br being preferred); and R represents (C₁-C₁₀)alkyl.

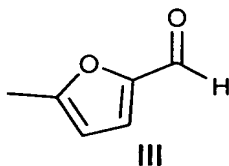
This invention is also directed at making a compound of formula **XI** or **XII**:



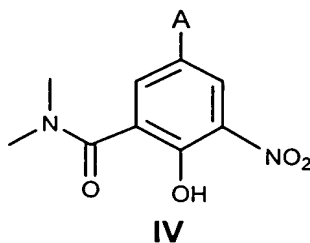
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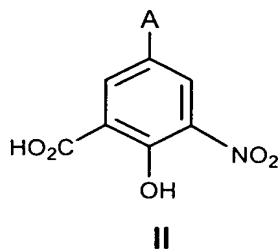
using a compound of formula **III**:



This invention is also directed to a process for making a compound of formula
IV

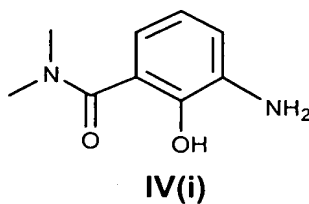


5 using a compound of formula **II**:

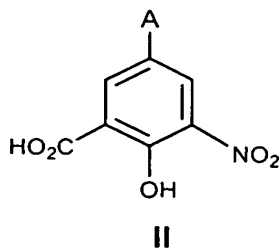


10 wherein A is selected from the group consisting of Br, Cl and I (with Br being preferred).

This invention is also directed to a process for making a compound of formula
IV(i):

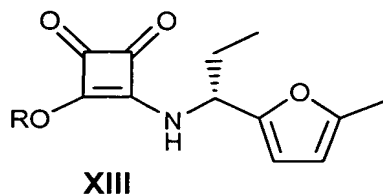


15 from a compound of formula **II**:

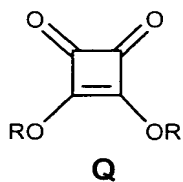


wherein A is selected from the group consisting of Br, Cl and I (with Br being preferred).

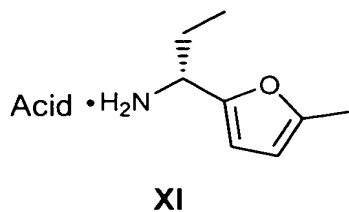
This invention is also directed to a process for making a compound of formula **XIII**:



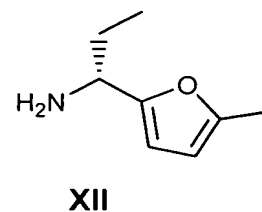
using compounds of the formulas **Q** and **XI**, or **Q** and **XII**:



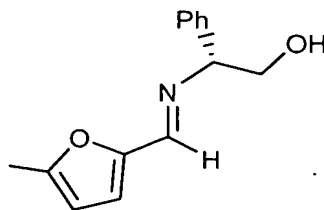
and



or

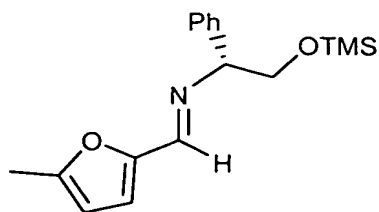


This invention is also directed to the intermediate compound



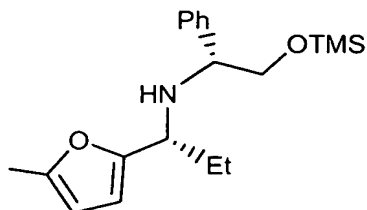
15 made during a process of this invention.

This invention is also directed to the intermediate compound



made during a process of this invention.

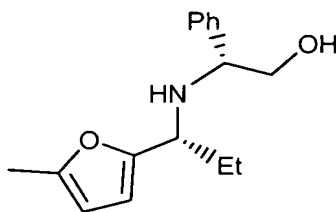
This invention is also directed to the intermediate compound



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made during a process of this invention.

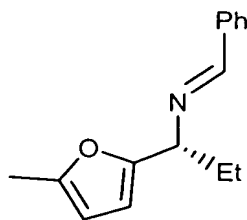
This invention is also directed to the intermediate compound



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made during a process of this invention.

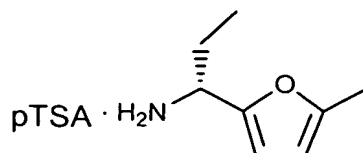
This invention is also directed to the intermediate compound



15

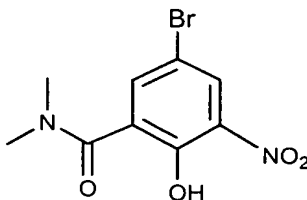
made during a process of this invention.

This invention is also directed to the intermediate compound



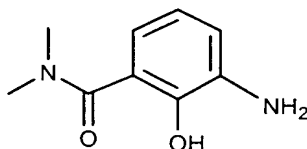
made during a process of this invention.

This invention is also directed to the intermediate compound



made during a process of this invention.

This invention is also directed to the intermediate compound



made during a process of this invention.

The inventive process to make the compound of formula I has several advantages: 5-bromo-3-nitrosalicylic acid is readily available and less expensive, there is no need to isolate the unstable reduction intermediate compound of formula IV(i), the compound of formula XI is more easily purified because no column chromatography is involved, and the salt formation of compound XI improved chiral purity of the amine.

Description of the Invention

As used herein, the following terms, unless otherwise indicated, have the following meanings:

"g" = grams.

"HPLC" = High Performance Liquid Chromatography.

"DBU" = 1,8-diazabicyclo[5.4.0]undec-7-ene.

"DMAP" = 4-dimethylaminopyridine.

"DME" = dimethylether.

"DMF" = N,N-dimethylformamide.

"DMSO" = dimethylsulfonic acid.

"MHz" = Megahertz.

"mL" = milliliters.

"Mp" = melting point.

5 "NMR" = nuclear magnetic resonance spectroscopy.

"THF" = tetrahydrofuran.

"TMS" = trimethylsilyl.

"TMSOTF" = trimethylsilyl-O-triflate.

"TBME" = T-butylmethyl ether.

10 "Alkyl" means an aliphatic hydrocarbon group, which may be straight or branched, and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a
15 linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain, which may be straight or branched. The term "substituted alkyl" means that the alkyl group is substituted by one or more substituents each independently selected from the group consisting of: halo, alkyl, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)₂,
20 carboxy and -C(O)O-alkyl. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, heptyl, nonyl, decyl, fluoromethyl, trifluoromethyl and cyclopropylmethyl.

"Alkenyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon double bond, which may be straight or branched, and comprising
25 about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have about 2 to about 12 carbon atoms in the chain, and more preferably about 2 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups, such as methyl, ethyl or propyl, are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 6 carbon atoms in the chain, which may be straight or
30 branched. The term "substituted alkenyl" means that the alkenyl group is substituted by one or more substituents each independently selected from the group consisting of: halo, alkyl, aryl, cycloalkyl, cyano, and alkoxy. Non-limiting examples of suitable

alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl.

"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond, which may be straight or branched, and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain, and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain, which may be straight or branched.

Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butylnyl, 3-methylbutynyl, n-pentynyl, and decynyl. The term "substituted alkynyl" means that the alkynyl group is substituted by one or more substituents each independently selected from the group consisting of: alkyl, aryl and cycloalkyl.

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more "ring system substituents", which may be the same or different, and are as defined herein. Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxaliny, phthalazinyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinoliny, imidazolyl, thienopyridyl,

quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like.

"Aralkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the alkyl.

"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described. Preferred alkylaryls comprise a lower alkyl group. Non-limiting examples of suitable alkylaryl groups include o-tolyl, p-tolyl and xylyl. The bond to the parent moiety is through the aryl.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents", which may be the same or different, and are as defined herein. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalin, norbornyl, adamantyl and the like.

"Halo" means fluoro, chloro, bromo, or iodo groups. Preferred are fluoro, chloro or bromo, and more preferred are fluoro and chloro.

"Halogen" means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine or bromine, and more preferred are fluorine and chlorine.

"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system, which, for example, replaces an available hydrogen on the ring system. Ring system substituents are each independently selected from the group consisting of: aryl, heteroaryl, aralkyl, alkylaryl, aralkenyl, heteroaralkyl, alkylheteroaryl, heteroaralkenyl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, Y₁Y₂N-, Y₁Y₂N-alkyl-,

$Y_1Y_2NC(O)-$ and $Y_1Y_2NSO_2-$, wherein Y_1 and Y_2 are each independently selected from the group consisting of hydrogen, alkyl, aryl, and aralkyl.

"Cycloalkenyl" means a non-aromatic mono or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms, which contains at least one carbon-carbon double bond. Preferred cycloalkenyl rings contain about 5 to about 7 ring atoms. The cycloalkenyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkenyls include cyclopentenyl, cyclohexenyl, cycloheptenyl, and the like. Non-limiting example of a suitable multicyclic cycloalkenyl is norbornenyl.

"Heterocyclenyl" means a non-aromatic monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur atom, alone or in combination, and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclenyl rings contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclenyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The heterocyclenyl can be optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined above. The nitrogen or sulfur atom of the heterocyclenyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic azaheterocyclenyl groups include 1,2,3,4- tetrahydropyridine, 1,2-dihydropyridyl, 1,4-dihydropyridyl, 1,2,3,6-tetrahydropyridine, 1,4,5,6-tetrahydropyrimidine, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolynyl, 2-pyrazolynyl, and the like. Non-limiting examples of suitable oxaheterocyclenyl groups include 3,4-dihydro-2H-pyran, dihydrofuranyl, fluorodihydrofuranyl, and the like. Non-limiting example of a suitable multicyclic oxaheterocyclenyl group is 7-oxabicyclo[2.2.1]heptenyl. Non-limiting examples of suitable monocyclic thiaheterocyclenyl rings include dihydrothiophenyl, dihydrothiopyranyl, and the like.

"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The heterocyclyl can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

"Aralkenyl" means an aryl-alkenyl- group in which the aryl and alkenyl are as previously described. Preferred aralkenyls contain a lower alkenyl group. Non-limiting examples of suitable aralkenyl groups include 2-phenethenyl and 2-naphthylethenyl. The bond to the parent moiety is through the alkenyl.

"Heteroaralkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl group. Non-limiting examples of suitable aralkyl groups include pyridylmethyl, 2-(furan-3-yl)ethyl and quinolin-3-ylmethyl. The bond to the parent moiety is through the alkyl.

"Heteroaralkenyl" means a heteroaryl-alkenyl- group in which the heteroaryl and alkenyl are as previously described. Preferred heteroaralkenyls contain a lower alkenyl group. Non-limiting examples of suitable heteroaralkenyl groups include 2-(pyrid-3-yl)ethenyl and 2-(quinolin-3-yl)ethenyl. The bond to the parent moiety is through the alkenyl.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Acyl" means an H-C(O)-, alkyl-C(O)-, alkenyl-C(O)-, alkynyl-C(O)-, cycloalkyl-C(O)-, cycloalkenyl-C(O)-, or cycloalkynyl-C(O)- group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl, propanoyl, 2-methylpropanoyl, butanoyl and cyclohexanoyl.

"Aroyl" means an aryl-C(O)- group in which the aryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include benzoyl and 1- and 2-naphthoyl.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and heptoxy. The bond to the parent moiety is through the ether oxygen.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Non-limiting examples of suitable aryloxy groups include phenoxy and naphthoxy. The bond to the parent moiety is through the ether oxygen.

"Aralkyloxy" means an aralkyl-O- group in which the aralkyl group is as previously described. Non-limiting examples of suitable aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy. The bond to the parent moiety is through the ether oxygen.

"Alkylamino" means an -NH₂ or -NH₃⁺ group in which one or more of the hydrogen atoms on the nitrogen are replaced by an alkyl group as defined above.

"Arylamino" means an -NH₂ or -NH₃⁺ group in which one or more of the hydrogen atoms on the nitrogen are replaced by an aryl group as defined above.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkylthio groups include methylthio, ethylthio, i-propylthio and heptylthio. The bond to the parent moiety is through the sulfur.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups include phenylthio and naphthylthio. The bond to the parent moiety is through the sulfur.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. Non-limiting example of a suitable aralkylthio group is benzylthio. The bond to the parent moiety is through the sulfur.

"Alkoxycarbonyl" means an alkyl-O-CO- group. Non-limiting examples of suitable alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aryloxycarbonyl" means an aryl-O-C(O)- group. Non-limiting examples of suitable aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aralkoxycarbonyl" means an aralkyl-O-C(O)- group. Non-limiting example of a suitable aralkoxycarbonyl group is benzyloxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Alkylsulfonyl" means an alkyl-S(O₂)- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfonyl.

"Alkylsulfinyl" means an alkyl-S(O)- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfinyl.

"Arylsulfonyl" means an aryl-S(O₂)- group. The bond to the parent moiety is through the sulfonyl.

"Arylsulfinyl" means an aryl-S(O)- group. The bond to the parent moiety is through the sulfinyl.

"Suitable temperature" means the temperature which results in a desirable rate of a reaction, and usually it is the temperature that results in an acceptable yield of the desired product with the minimum production of undesirable products; or a "suitable temperature" is that temperature at which reagents can be safely mixed together, or that temperature at which a reaction mixture can be safely controlled, or that temperature at which the desired products are isolated from solution.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product

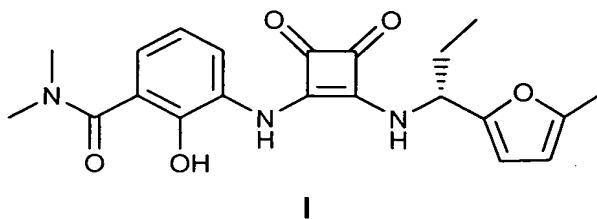
which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

"Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolable solvates. Non-limiting examples of suitable solvates include ethanlates, methanlates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H₂O.

The embodiments described below are numbered for purposes of reference only.

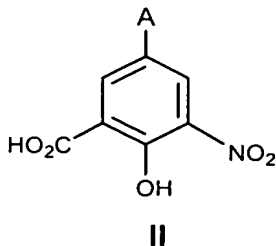
The reagents and reaction conditions used, as described below, to make a particular compound in a particular step in the process for making the compound of formula I, are also applicable to any embodiment directed to a process for making that particular compound.

Embodiment No. 1 of this invention is directed to a process for making the compound of formula I:

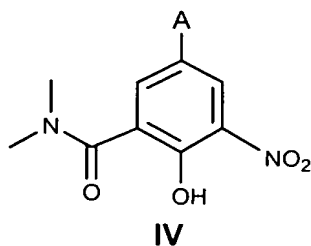


comprising:

(a) converting the compound of formula II



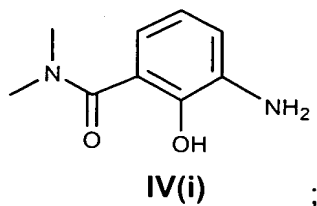
to a compound of formula IV:



wherein A, in compounds of formulas **II** and **IV**, is selected from the group consisting of Br, Cl and I (preferably Br);

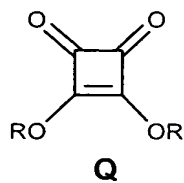
5

(b) hydrogenating the compound of formula **IV** with a suitable hydrogenation catalyst under hydrogen pressure, to form the intermediate compound of formula **IV(i)**:

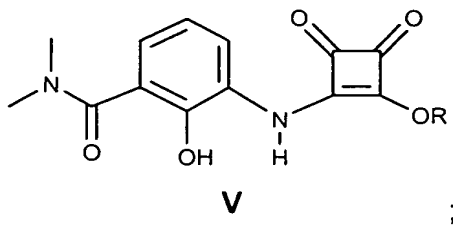


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(c) reacting the compound of formula **IV(i)** with a compound of formula **Q**:

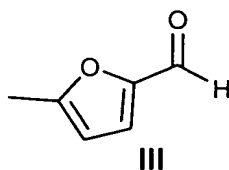


wherein R represents (C₁-C₁₀)alkyl, to yield a compound of formula **V**:

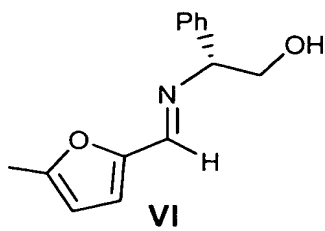


15

(d) converting the compound of formula **III**

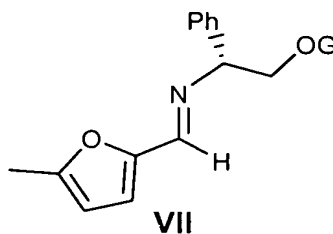


to a compound of formula **VI**:



5

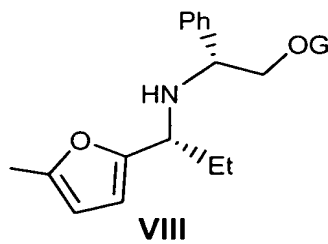
(e) adding a protecting group to the compound of formula **VI** to yield a compound of formula **VII**:



10

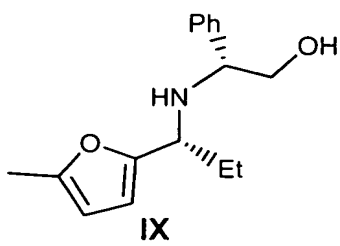
wherein G represents a protecting group;

(f) reacting the compound of formula **VII** with a suitable organometallic reagent, followed by work-up, to yield a compound of formula **VIII**:

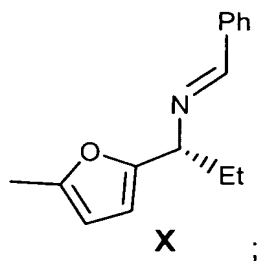


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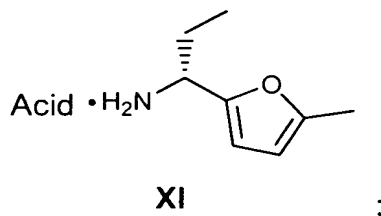
(g) removing the protecting group (G) from the compound of formula **VIII** to yield a compound of formula **IX**:



5 (h) converting the compound of formula **IX** into an imine intermediate compound of formula **X**:



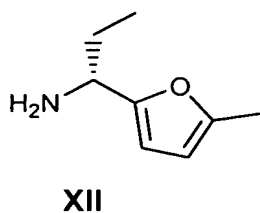
10 (i) converting the imine intermediate compound of formula **X** into the salt of formula **XI**:



(j) reacting the compound of formula **XI** with the compound of formula **V** to yield the compound of formula **I**; or

15

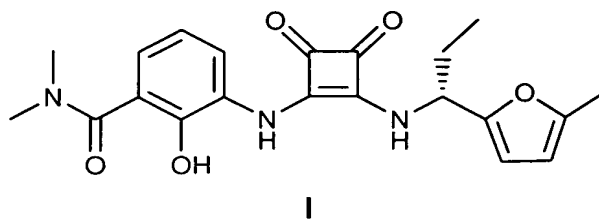
(k) converting the compound of formula **XI** to the free amine:



and reacting the compound of formula **XII** with the compound of formula **V** to yield the compound of formula **I**.

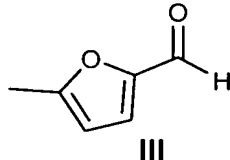
Those skilled in the art will appreciate that in the process of Embodiment No. 1, the order of making the compound of formula **V** and the compound of formula **XI** is not critical. Also the order of making the compound of formula **V** and the compound of formula **XII** is not critical.

Embodiment No. 2 of this invention is directed to a process for making the compound of formula **I**:

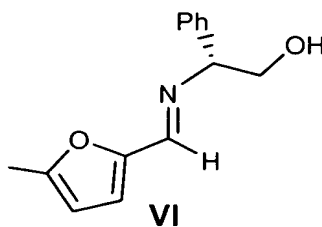


comprising:

(a) converting the compound of formula **III**

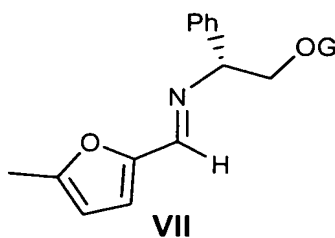


to a compound of formula **VI**:



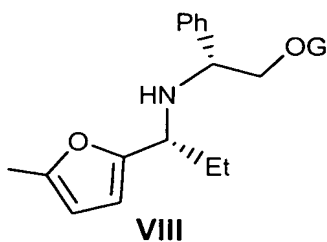
;

(b) adding a protecting group to the compound of formula **VI** to yield a compound of formula **VII**:



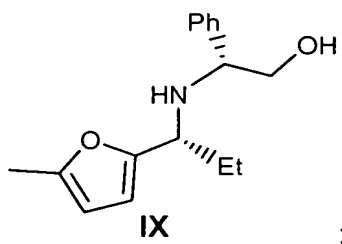
5 wherein G represents a protecting group;

(c) reacting the compound of formula **VII** with a suitable organometallic reagent, followed by work-up, to yield a compound of formula **VIII**:



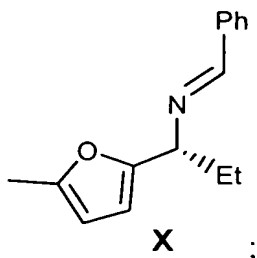
10

(d) removing the protecting group (G) from the compound of formula **VIII** to yield a compound of formula **IX**:

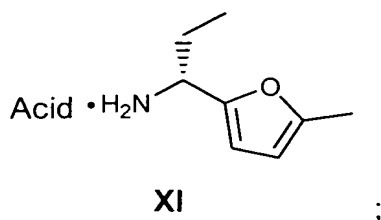


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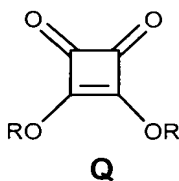
(e) converting the compound of formula **IX** into an imine intermediate compound of formula **X**:



5 (f) converting the imine intermediate compound of formula **X** into the salt of formula **XI**:

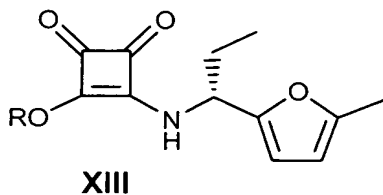


(g) reacting the compound of formula **XI** with the compound of formula **Q**:



10

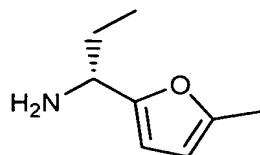
to yield a compound of formula **XIII**:



wherein R represents (C₁-C₁₀)alkyl in formulas **Q** and **XIII**; or

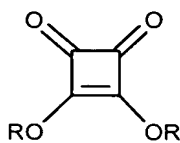
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(h) converting the compound of formula **XI** to a compound of formula **XII**:



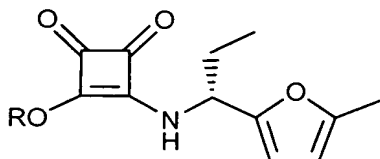
XII

and reacting the compound of formula **XII** with a compound of formula **Q**:



Q

to yield a compound of formula **XIII**:

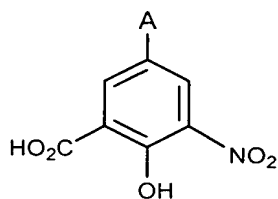


XIII

5

wherein R represents (C₁-C₁₀)alkyl in formulas **Q** and **XIII**;

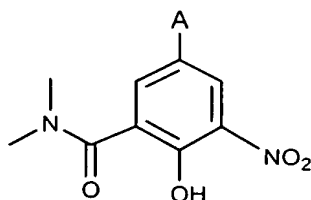
(i) converting the compound of formula **II**



II

10

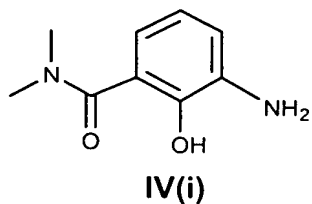
wherein A is selected from the group consisting of Br, Cl and I (preferably Br), to a compound of formula **IV**:



IV

;

(j) hydrogenating the compound of formula **IV** with a suitable hydrogenation catalyst under hydrogen pressure, to form the intermediate compound of formula **IV(i)**:



5 (k) reacting the compound of formula **IV(i)** with the compound of formula **XIII** to yield the compound of formula **I**.

Those skilled in the art will appreciate that in the process of Embodiment No. 2, the order of making the compound of formula **XIII** and the compound of formula **IV(i)** is not critical.

The reagents and reaction conditions used to make the compound of formula **XI** from the compound of formula **III** in steps (a) to (f) in Embodiment No. 2 are the same as those used to make the compound of formula **XI** from the compound of formula **III** in steps (d) to (i) in Embodiment No. 1.

15 The reagents and reaction conditions to convert the salt of formula **XI** to the free amine of formula **XII** in step (h) of Embodiment No. 2 are the same as those used to convert the salt of formula **XI** to the free amine of formula **XII** in step (k) of Embodiment No. 1.

20 The reagents and reaction conditions to make the compound of formula **XIII** from the compound of formula **XI** in step (g) of Embodiment No. 2 are the same as those used to make the compound of formula **I**, from the compounds of formulas **V** and **XI**, in step (j) of Embodiment No. 1.

25 The reagents and reaction conditions to make the compound of formula **XIII** from the compound of formula **XII** in step (h) of Embodiment No. 2 are the same as those used to make the compound of formula **I**, from the compounds of formula **V** and **XII**, in step (k) of Embodiment No. 1.

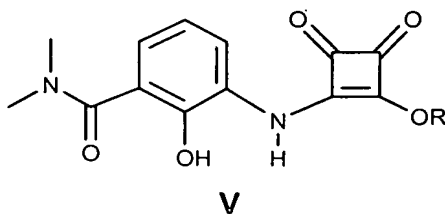
Embodiment No. 3 is directed to the process described in Embodiment No. 1 wherein the compound of formula **XI** is reacted with the compound of formula **V** to yield the compound of formula **I**.

Embodiment No. 4 is directed to the process described in Embodiment No. 1 wherein the compound of formula **XI** is converted to the free amine of formula **XII**, and said compound of formula **XII** is reacted with the compound of formula **V** to yield the compound of formula **I**.

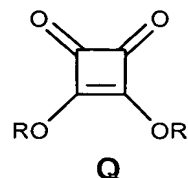
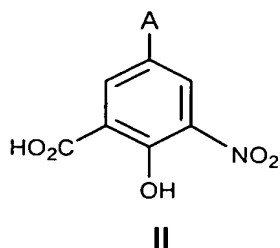
Embodiment No. 5 is directed to the process described in Embodiment No. 2 wherein the compound of formula **XI** is reacted with the compound of formula **Q** to yield the compound of formula **XIII**.

Embodiment No. 6 is directed to the process described in Embodiment No. 2 wherein the compound of formula **XI** is converted to the free amine of formula **XII**, and said compound of formula **XII** is reacted with the compound of formula **Q** to yield the compound of formula **XIII**.

Embodiment No. 7 is directed to a process for making a compound of formula **V**:

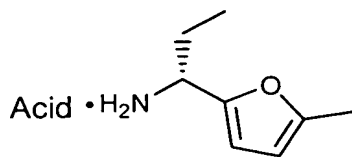


using compounds of the formulas **II** and **Q**:



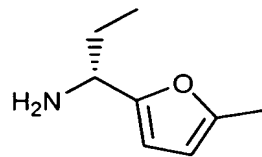
wherein A is selected from the group consisting of Br, Cl and I (with Br being preferred); and R represents (C₁-C₁₀)alkyl. The reagents and reaction conditions used in this embodiment are the same as those used in the preparation of the compound of formula **V** from compounds of formulas **II** and **Q** described in Embodiment No. 1 steps (a) to (c).

Embodiment No. 8 is directed to a process for making a compound of formula **XI** or **XII**:



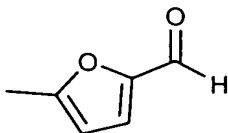
XI

or



XII

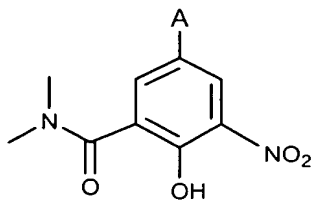
5 using a compound of formula **III**:



III

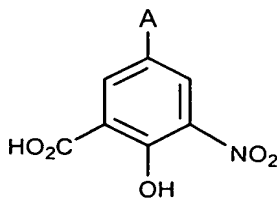
The reagents and reaction conditions used in this embodiment are the same as those used in the preparation of the compound of formula **XI** or **XII** from compound of formula **III** described in Embodiment No. 1 steps (d) to (i), and, for **XII**, the conversion step in step (k).

Embodiment No. 9 is directed to a process for making a compound of formula **IV**



IV

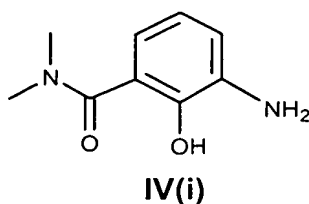
15 using a compound of formula **II**:



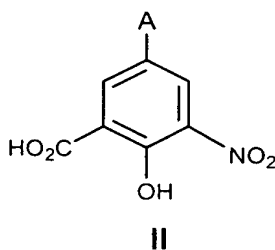
II

wherein A is selected from the group consisting of Br, Cl and I (with Br being preferred). The reagents and reaction conditions used in this embodiment are the same as those used in the preparation of the compound of formula **IV** from compound of formula **II** described in Embodiment No. 1 step (a).

Embodiment No. 10 is directed to a process for making a compound of formula **IV(i)**:

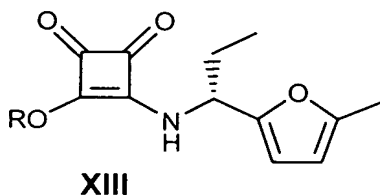


from a compound of formula **II**:

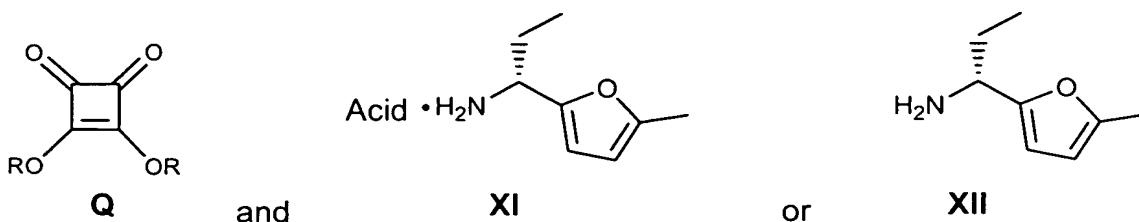


wherein A is selected from the group consisting of Br, Cl and I (with Br being preferred). The reagents and reaction conditions used in this embodiment are the same as those used in the preparation of the compound of formula **IV(i)** from compound of formula **II** described in Embodiment No. 1 steps (a) and (b).

Embodiment No. 11 is directed to a process for making a compound of formula **XIII**:

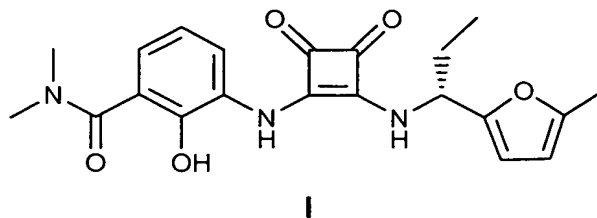


using compounds of the formulas **Q** and **XI**, or **Q** and **XII**:



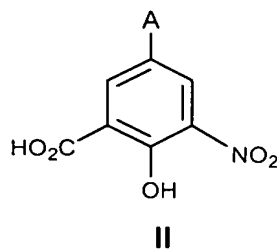
The reagents and reaction conditions used in this embodiment are the same as those used in the preparation of the compound of formula **XIII** from compounds of formulas **Q** and **XI**, or **Q** and **XII**, described in Embodiment No. 2 steps (a) to (h).

Embodiment No. 12 is directed to a process for preparing a compound of formula **I**:



comprising:

(a) dissolving the compound of formula **II**:



in:

a solvent selected from the group consisting of: acetonitrile, THF, t-butylmethylether, methylenechloride, toluene, ethylacetate, diethylether, and chloroform, and

an acid chloride selected from the group consisting of: thionyl chloride and oxalyl chloride, wherein a catalytic amount of DMF is optionally used when oxalyl chloride is used;

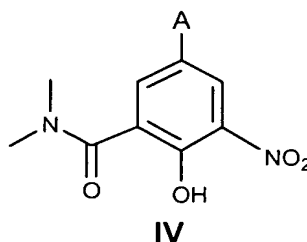
and adjusting the temperature of the resulting reaction mixture to a about -20°C to about 110°C;

cooling the reaction mixture, when the reaction is complete, to a temperature of about 5°C to about 10°C;

adding dimethylamine gas or a solution of dimethylamine, at a concentration of at least about 1 molar equivalent with respect to the compound of formula II, wherein
5 the solvent for said dimethylamine solution is selected from the group consisting of: acetonitrile, THF, t-butylmethylether, methylenechloride, toluene, ethylacetate, diethylether, and chloroform;

adjusting the temperature of the resulting reaction mixture to a temperature of about -20°C to about 50°C;

10 acidifying the resulting reaction mixture with an aqueous acid to a pH of about 0 to about 7, to produce a compound of formula IV:



wherein A is in the compounds of formulas II and IV is selected from the group
15 consisting of Br, Cl and I;

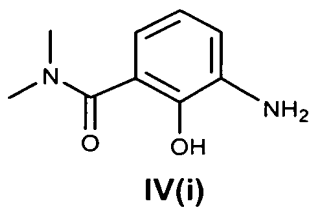
(b) hydrogenating the compound of formula IV by mixing said compound of formula IV with:

a base selected from the group consisting of: KOH, NaOH, Na₂CO₃, K₂CO₃,
20 K₂CO₃, NaHCO₃, KHCO₃, tetramethylguanidine, DBU, diisopropylethylamine and mixtures thereof, wherein said base is in a concentration of at least about 1 molar equivalent with respect to the compound of formula IV,

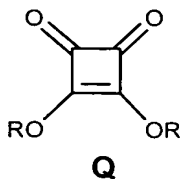
a hydrogenation catalyst selected from the group consisting of: Pd/C, Pt/C, PdOH, and Raney nickel; and

25 a solvent selected from the group consisting of: THF, methanol, ethanol, propanol, isopropanol, acetonitrile, ethyl acetate, and mixtures thereof; and

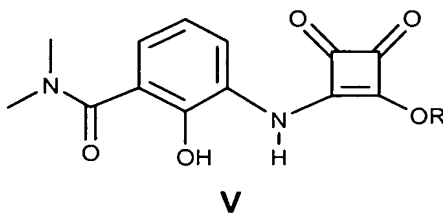
pressurizing the resulting mixture under hydrogen at a pressure of about 10 to about 500 psi to produce the intermediate compound of formula IV(i):



(c) adding the compound of formula **Q**:



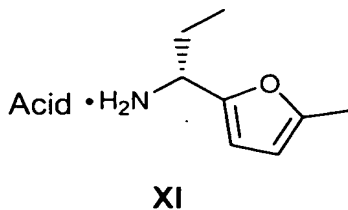
5 in a concentration of at least 1 molar equivalent with respect to the compound of formula **IV(i)**, to the reaction mixture comprising the compound of formula **IV(i)** obtained in step (b), and adjusting the temperature to about 0 °C to about 80 °C to produce a compound of formula **V**:



10 wherein R in said compound of formula **Q** is selected from the group consisting of: methyl, ethyl, propyl and isopropyl, and wherein said reaction is optionally catalyzed by a base selected from the group consisting of: KOH, NaOH, Na₂CO₃, K₂CO₃, NaHCO₃, KHCO₃, tetramethylguanidine, DBU, diisopropylethylamine, and mixtures thereof;

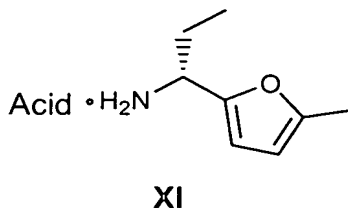
15

(d1) mixing: the compound of formula **V** from step (c) with the compound of formula **XI**



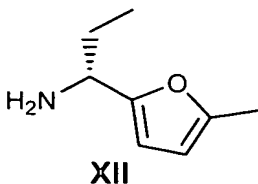
and a base in a solvent, heating the resulting reaction mixture to a temperature of about 20 °C to about 150 °C, and then acidifying the reaction mixture to a pH of about 3 to about 7, to produce a compound of formula I; said base being selected from the group consisting of: pyridine, dimethylaminopyridine (DMAP), diisopropylethylamine and -N(R²)₃; wherein each R² is independently selected from the group consisting of: alkyl and cycloalkyl; and said base being used in a concentration of at least about 1 molar equivalent with respect to the compound of formula IV; and said solvent being selected from the group consisting of: nitrile, ether, and alcohol solvents; or

(d2) mixing the compound of formula XI:



with water and solvent selected from the group consisting of: ethers and methylene chloride;

basifying the resulting reaction mixture with a base selected from the group consisting of: NaOH, KOH, Mg(OH)₂, Na₂CO₃ and K₂CO₃, to a pH of about 7 to about 14, said basification being done at a temperature of about 0°C to about 50 °C to produce a compound of formula XII:



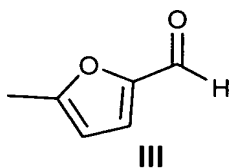
dissolving said compound of formula V from step (c) in a solvent selected from the group consisting of: alcohol solvents, nitrile solvents, ether solvents and toluene;

mixing the resulting solution with the compound of formula XII, and optionally adding a catalytic amount of a base to the resulting solution, wherein said base is

selected from the group consisting of: pyridine and $-N(R^3)_3$, wherein R^3 is selected from the group consisting of: alkyl, aryl, aralkyl, and arylalkyl, and wherein the temperature of the resulting solution is about 10°C to about 150°C , to produce a compound of formula I;

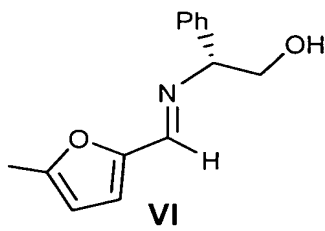
5

(e) wherein said compound of formula **XI** is prepared by:
mixing the compound of formula **III**:



10 with 0.01 molar equivalent, with respect to the compound of formula **III**, of
R-2-(-)-phenylglycinol in a solvent selected from the group consisting of: aromatic
solvents, halogenated solvents, alcohol solvents, nitrile solvents, ether solvents, and
mixtures thereof, and heating the resulting mixture at reflux to produce a compound of
formula **VI**:

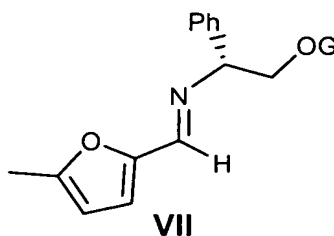
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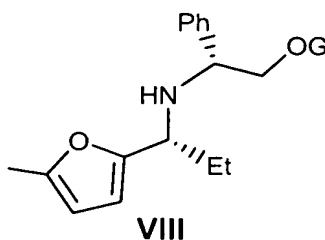
mixing the solution comprising the compound of formula **VI** with a silylating
reagent selected from the group consisting of: hexamethyldisilazane, TMS chloride,
20 and TMSOTF, wherein the TMS chloride or TMSOTF is used in combination with an
aryl or alkyl base, and an acid in a concentration of at least about 0.2 molar equivalent
with respect to the compound of formula **VI**, preferably at least about 0.4 molar
equivalents, said acid being selected from the group consisting of: ammonium
sulphate, ammonium nitrate, ammonium chloride, H_2SO_4 , HCl , H_3PO_4 , citric acid,
25 mesyl chloride, paratoluenesulfonic acid, paratoluenesulfonic acid pyridinium salt, and

alkylsulfonic acid, and heating the resulting reaction mixture at reflux to produce an imine compound of formula **VII**:

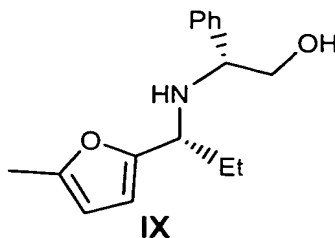


5 wherein G represents a protecting group that is the silylating reagent used;

mixing said imine compound of formula **VII** with an organometallic reagent in a solvent at a temperature of about 0 °C to about 80 °C, said organometallic reagent being selected from the group consisting of: diethyl zinc, ethylzinc bromide, ethylzinc chloride, ethylmagnesium bromide, ethylmagnesium chloride and ethyllithium, said
10 organometallic reagent being used in a concentration of 0.1 to about 5 molar equivalents with respect to the compound of formula **VII**, said solvent being selected from the group consisting of: benzene, toluene, TBME, THF, DME, dimethoxyethane, and mixtures thereof, to produce a compound of formula **VIII**:



15 adding the compound of formula **VIII** to a cooled aqueous acid, said acid being at a concentration of about 2.5 to about 5 molar equivalents with respect to the compound of formula **VIII**, adding water and a cosolvent and mixing the resulting mixture, adding a base to said mixture to adjust the pH of the aqueous phase to about
20 9 to about 13, to produce a compound of formula **IX**:



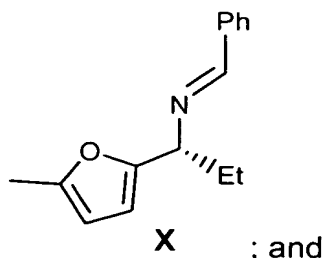
said co-solvent being selected from the group consisting of: methanol, ethanol, propanol, isopropanol, butanol, sec-butanol, pentanol, hexanol, heptanol, octanol, and mixtures thereof,

5 said base being selected from the group consisting of: ammonium hydroxide, metal hydroxide, metal oxide, metal carbonate, metal bicarbonate, and mixtures thereof, wherein said metal is selected from the group consisting of: lithium, sodium, potassium, rubidium, cesium, beryllium, magnesium, calcium, strontium, barium, aluminum, indium, thallium, titanium, zirconium, cobalt, copper, silver, zinc cadmium, mercury and cerium, or

10 said base being selected from the group consisting of: a metal salt of a (C₁-C₁₂)alkanol and a (C₃-C₁₂)cycloalkanol, wherein the metal is selected from the group consisting of: Li, Na, K, and Mg;

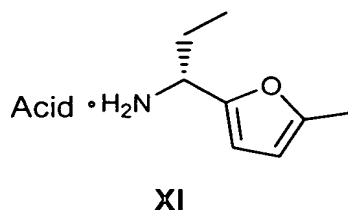
15 dissolving the compound of formula IX in solvent selected from the group consisting of: water, methanol, ethanol, propanol, isopropanol, butanol, sec-butanol, pentanol, hexanol, tetrahydrofuran, 1,2-dimethoxyethane, 1,2-diethoxymethane, diglyme, 1,4-dioxane, and mixtures thereof,

20 cooling the resulting solution to a temperature of about -5 °C to about 20 °C, adding R⁴NH₂ to said solution, and then adding an agent selected from the group consisting of: NaIO₄, Pb(OAc)₄, H₅IO₆, and mixtures thereof, to produce a compound of **X**:



wherein R^4 is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and aralkyl;

dissolving the compound of formula **X** in a solvent and adding the resulting solution to an acid solution at a temperature ranging preferably from about -50 °C to about 80 °C to produce the compound of formula **XI**:



said compound **XI** being a salt,

wherein said solvent is selected from the group consisting of: hydrocarbon solvents and ethers and mixtures thereof, and

said acid is selected from the group consisting of: sulfonic acids, tartaric acids, H_2SO_4 , HCl , H_3PO_4 , HBr , carboxylic acids and mixtures thereof.

Embodiment No. 13 is directed to a process as described in Embodiment No. 12 except that:

in step (a), the preparation of the compound of formula **IV**, the reaction mixture of said compound of formula **II** and said acid chloride is 40°C to about 90°C, said dimethylamine is at a concentration of at least about 2 molar equivalents with respect to the compound of formula **II**, said temperature of said reaction mixture is about 0°C to about 25°C, said reaction mixture is acidified to a pH of about 1 to about 5, said acid for said aqueous acid is selected from the group consisting of: HCl , H_2SO_4 , H_3PO_4 , and mixtures thereof;

in step (b), the hydrogenation of the compound of formula **IV**, said base is selected from the group consisting of: Na_2CO_3 , K_2CO_3 , and mixtures thereof, said base is used at a concentration of about 1.05 to about 1.5 molar equivalents, said catalyst is selected from the group consisting of Pd/C and $PdOH$, said solvent is selected from the group consisting of: methanol, ethanol, propanol, isopropanol, and mixtures thereof, and said hydrogen pressure is about 20 to about 200 psi;

in step (c), the reaction of the compound of formula **Q** with the compound of formula **IV(i)**, the compound of formula **Q** is used at a concentration of about 1 to about 2 molar equivalents, said temperature is about 20 °C to about 50 °C, and said optional base is selected from the group consisting of: Na₂CO₃, K₂CO₃ and mixtures thereof;

in step (d1), the reaction of the compound of formula **V** with the compound of formula **XI**, said base is used in an amount of about 1 to about 2 molar equivalents with respect to the compound of formula **V**, said solvent is selected from the group consisting of alcohol and nitrile solvents, said temperature is about 40 °C to about 80 °C, and said pH is about 3 to about 5;

in step (d2), the reaction of the compound of formula **V** with the compound of formula **XII**:

said mixture with said compound of formula **XI** is basified with NaOH or KOH to a pH of about 10 to about 14 at a temperature of about 10 °C to about 40 °C to produce said compound of formula **XII**,

said compound of formula **V** is dissolved in alcohol solvent, said compound of formula **XII** being used at a concentration about 1 molar equivalent with respect to the compound of formula **V**,

said catalytic base being selected from the group consisting of: pyridine and -N(R³)₃ wherein each R³ is independently selected from the group consisting of ethyl, isopropyl, propyl, butyl, phenyl, tolyl and benzyl, and

said temperature of said resulting solution with the compound of formula **XII** being about 40 °C to about 80 °C;

in step (e), in the reaction to produce the compound of formula **VI** from the compound of formula **III**, said R-2-(-)-phenylglycinol is in a concentration of about 0.5 to about 1.5 molar equivalents, and said solvent for said R-2-(-)-phenylglycinol is selected from the group consisting of: benzene, toluene, dichloromethane, methylene chloride, chlorobenzene, methanol, ethanol, propanol, isopropanol, n-propanol, butanol, acetonitrile, THF and t-butylmethylether;

in step (e) in the reaction to produce the compound of formula **VII** from the compound of formula **VI**, said silylating reagent is selected from the group consisting of: hexamethyldisilazane, TMS chloride, and TMSOTf, wherein the TMS

chloride or TMSOTF is used in combination with triethylamine, and said acid is selected from the group consisting of: ammonium sulphate, ammonium nitrate and ammonium chloride, said acid at a concentration of at least about 0.4 molar equivalents with respect to the compound of formula **VI**;

5 in step (e), in the reaction to produce the compound of formula **VIII** from the compound of formula **VII**, said organometallic reagent is used in a concentration of about 1 to about 5 molar equivalents with respect to the compound of formula **VII**, said solvent is selected from the group consisting of: THF, TBME, and mixtures thereof, and said temperature is about about 10 °C to about 50 °C;

10 in step (e), in the reaction to produce the compound of formula **IX** from the compound of formula **VIII**, said cooled aqueous acid is at a temperature of about 0 °C to about 15 °C, said acid is selected from the group consisting of: H₂SO₄, HCl, H₃PO₄, and mixtures thereof, said acid is in a concentration of about about about 2.5 to about 3 molar equivalents with respect to the compound of formula **VIII**, said
15 cosolvent is selected from the group consisting of: methanol, ethanol, propanol, isopropanol, butanol, sec-butanol, pentanol, hexanol, heptanol, octanol, and mixtures thereof, said base is selected from the group consisting of: KOH, NaOH, NH₄OH, LiOH and CsOH, and said pH is adjusted to about 10 to about 11,

20 in step (e), in the reaction to produce the compound of formula **X** from the compound of formula **IX**, the resulting solution is cooled to about 0 °C to about 15 °C, and said R⁴ is a (C₁-C₃)alkyl; and

25 in step (e), in the reaction to produce the compound of formula **XI** from the compound of formula **X**, said compound of formula **XI** is dissolved in a solvent selected from the group consisting of: toluene, xylene, chlorobenzene, dichlorobenzene, diethyl ether, dipropyl ether and dibutyl ether, 1,2-dimethoxyethane, 1,2-diethoxyethane, diglyme, 1,4-dioxane, tetrahydrofuran and mixtures thereof, said acid in said acid solution is selected from the group consisting of: paratoluene sulfonic acid and alkylsulfonic acids, and said temperature is about -20 °C to about 20 °C.

30 Embodiment No. 14 is directed to a process as described in Embodiment No. 13 except that:

 in step (a), the preparation of the compound of formula **IV**, said compound of formula **II** is dissolved in acetonitrile and thionyl chloride, said

temperature is about 65°C to about 75°C, said dimethylamine is dissolved in acetonitrile, said dimethylamine being at a concentration of about 2.5 molar equivalents with respect to the compound of formula II, said temperature of said reaction mixture is about 5°C to about 10°C, said reaction mixture is acidified to a pH of about 2 to about 3, said aqueous acid is H₂SO₄, and said substituent A is Br;

in step (b), the hydrogenation of the compound of formula IV, said base is K₂CO₃ used at a concentration of about 1.05 to about 1.1 molar equivalents, said catalyst is Pd/C, said solvent is ethanol, and said hydrogen pressure is about 100 to about 120 psi;

in step (c), the reaction of the compound of formula Q with the compound of formula IV(i), the compound of formula Q is used at a concentration of about 1.3 to about 1.5 molar equivalents, said temperature is about 25 °C to about 35 °C, R is ethyl, and said optional base is K₂CO₃;

in step (d1), the reaction of the compound of formula V with the compound of formula XI, the compound of formula XI is used in an amount of about 1.1 molar equivalents, said base is triethylamine used in an amount of about 1.3 to about 1.5 molar equivalents with respect to the compound of formula V, said solvent is acetonitrile, said temperature is about 60 °C to about 70 °C, and said pH is about 4;

in step (d2), the reaction of the compound of formula V with the compound of formula XII, said solvent used with said compound of formula XI is t-butyl methyl ether, said mixture with said compound of formula XI is basified with NaOH to a pH of about 12.5 to about 13.5 at a temperature of about 20 °C to about 30 °C to produce said compound of formula XII, said compound of formula V is dissolved in the solvent n-propanol, said compound of formula XII being used at a concentration about 1.1 molar equivalents with respect to the compound of formula V, said catalytic base being diisopropylethylamine, said temperature of said resulting solution with the compound of formula XII being about 60 °C to about 70 °C

in step (e), in the reaction to produce the compound of formula VI from the compound of formula III, said R-2-(-)-phenylglycinol is in a concentration of about 0.9 to about 1.1 molar equivalents, and said solvent for said R-2-(-)-phenylglycinol is THF;

in step (e) in the reaction to produce the compound of formula **VII** from the compound of formula **VI**, said silylating reagent is hexamethyldisilazane, and said acid is ammonium sulphate at a concentration of at least about 0.5 molar equivalents with respect to the compound of formula **VI**;

5 in step (e), in the reaction to produce the compound of formula **VIII** from the compound of formula **VII**, said organometallic reagent is ethylmagnesium bromide used in a concentration of about 2 to about 3 molar equivalents with respect to the compound of formula **VII**, said solvent is TBME, and said temperature is about 20 °C to about 35 °C;

10 in step (e), in the reaction to produce the compound of formula **IX** from the compound of formula **VIII**, said cooled aqueous acid is at a temperature of about 0 °C to about 10 °C, said acid is H₂SO₄, said acid is in a concentration of about about 2.5 molar equivalents with respect to the compound of formula **VIII**, said cosolvent is sec-butanol, said base is NH₄OH, and said pH is adjusted to about 11,

15 in step (e), in the reaction to produce the compound of formula **X** from the compound of formula **IX**, said compound of formula **IX** is dissolved in ethanol and the resulting solution is cooled to about 0 °C to about 10 °C, said R⁴ is methyl, and said agent is NaIO₄; and

20 in step (e), in the reaction to produce the compound of formula **XI** from the compound of formula **X**, said compound of formula **XI** is dissolved in THF, said acid in said acid solution is paratoluene sulfonic acid, and said temperature is about 0 °C to about 10 °C.

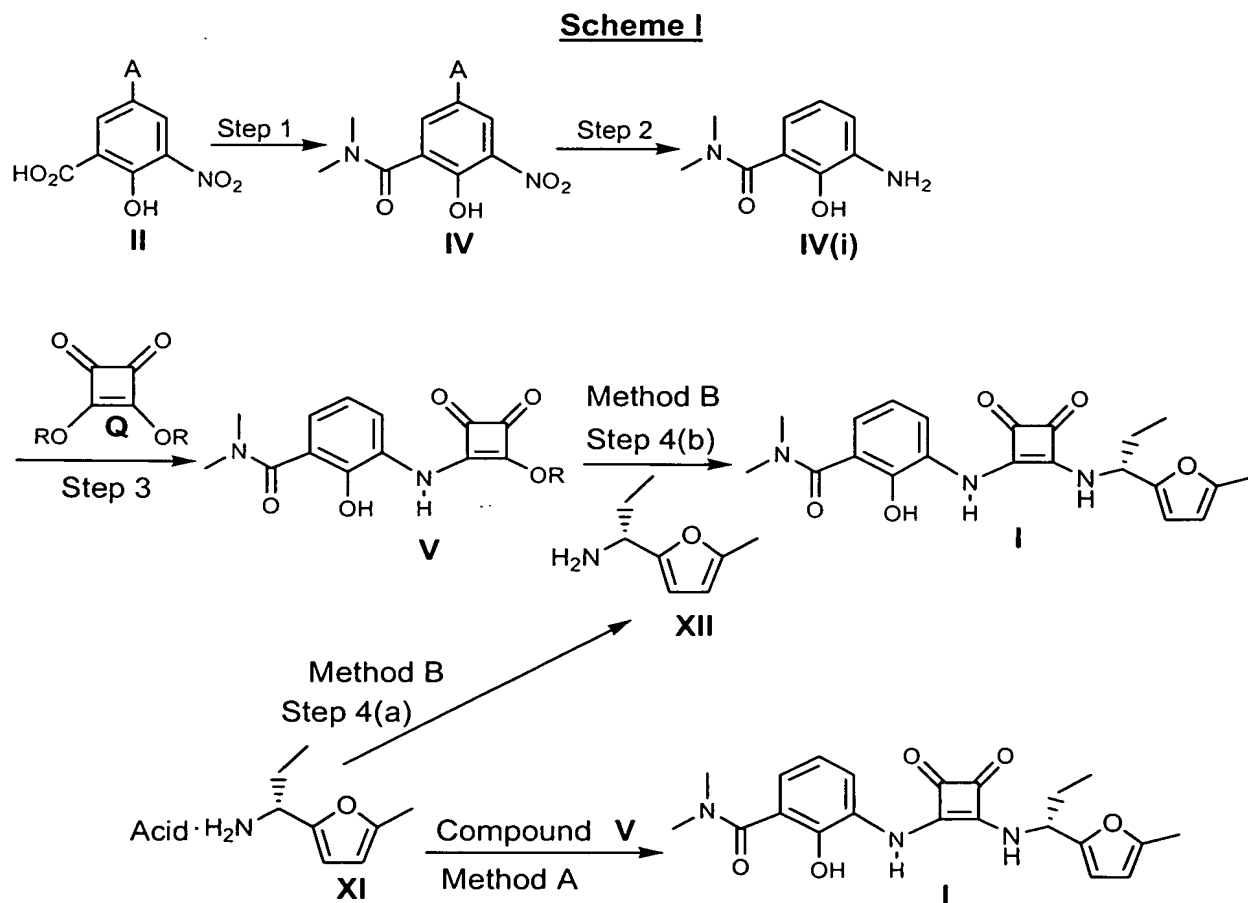
The protecting group G is selected from the group consisting of: silylating
25 reagents and esters (i.e., moieties having the formula R¹-C(O)-O-). Suitable silylating reagents include hexamethyldisilazane, TMS chloride, TMSOTF, and the like, wherein the TMS chloride or TMSOTF is used in combination with an aryl or alkyl base. Preferred silylating agents include hexamethyldisilazane, TMS chloride, TMSOTF, wherein the TMS chloride or TMSOTF is used in combination with
30 triethylamine. More preferably, the silylating agent is hexamethyldisilazane. R¹ is selected from the group consisting of: alkyl (e.g., methyl, ethyl and isopropyl), aryl (e.g., phenyl), and cycloalkyl (e.g., cyclopropyl and cyclohexyl). When an ester is

used then diethyl zinc is used to produce the compound of formula VIII from the compound of formula VII. The ester protecting group can be removed by basic hydrolysis wherein the base is a metal hydroxide, such as, for example, NaOH, KOH, LiOH and Ba(OH)₂.

5 Compound **XI** is the (R)-isomer. Those skilled in the art will appreciate that if the (S)-isomer were to be used the other enantiomer of formula **I** would be obtained.

The processes of this invention (for example the processes of Embodiment Nos. 1, 3, 4, 7, 8, 9 and 10) are described in Schemes **I** and **II** below.

10



Step 1:

15

The compound of formula **II** is dissolved in a suitable solvent and a suitable acid chloride. Non-limiting examples of suitable solvents preferably include

acetonitrile, THF, t-butylmethylether, methylenechloride, toluene, ethylacetate, diethylether, chloroform, and toluene, and more preferably acetonitrile. Non-limiting examples of suitable acid chlorides include thionyl chloride and oxalyl chloride, preferably thionyl chloride. If oxalyl chloride is used, a catalytic amount of DMF is also preferably used. The resulting mixture is stirred at a temperature ranging from about -20°C to about 110°C, preferably from about 40°C to about 90°C, most preferably from about 65°C to about 75°C, for about 2 hours or until the reaction is complete. The range of temperatures above can vary depending on which solvent is used. The reaction mixture is then cooled to a temperature ranging from about 5°C to about 10°C, and dimethylamine gas or a solution of dimethylamine in a suitable solvent is added slowly for over about one hour or until the reaction is complete. Non-limiting examples of suitable solvents which can be added to the dimethylamine include acetonitrile, THF, t-butylmethylether, methylenechloride, toluene, ethylacetate, diethylether, and chloroform, and preferably acetonitrile. The dimethylamine can be used generally at a concentration of at least about 1 molar equivalent with respect to the compound of formula II, preferably at least about 2 molar equivalents, and even more preferably about 2.5 molar equivalents. The reaction mixture is then adjusted to a temperature ranging from about -20°C to about 50°C, preferably from about 0°C to about 25°C, more preferably from about 5°C to about 10°C, for about 3 hours or until the reaction is complete. The mixture is then acidified with an aqueous acid to a pH ranging from about 0 to about 7, preferably from about 1 to about 5, more preferably from about 2 to about 3. Non-limiting examples of aqueous acids include HCl, H₂SO₄ or H₃PO₄, and the like, or mixtures thereof, preferably HCl, H₂SO₄, or mixtures thereof, more preferably H₂SO₄. The product of step 1 is the compound of formula IV which can be purified preferably by crystallization.

Preparation of the compound of formula V

Step 2:

A mixture is prepared containing the compound of formula IV from step 1, a base, a hydrogenation catalyst, and a solvent. Non-limiting examples of suitable bases include KOH, NaOH, Na₂CO₃, K₂CO₃, NaHCO₃, KHCO₃, tetramethylguanidine, DBU, diisopropylethylamine, and the like, or mixtures thereof, more preferably

Na₂CO₃, K₂CO₃, or mixtures thereof, most preferably K₂CO₃. Non-limiting examples of hydrogenation catalysts include Pd/C, Pt/C, PdOH, or Raney nickel, preferably Pd/C or PdOH, and more preferably Pd/C. Non-limiting examples of suitable solvents include THF, methanol, ethanol, propanol, isopropanol, acetonitrile, ethyl acetate, and the like, or mixtures thereof, preferably methanol, ethanol, propanol, isopropanol, or mixtures thereof, and more preferably ethanol. The base can be used generally in at least about 1 molar equivalent with respect to the compound of formula **IV**, preferably from about 1.05 to about 1.5 molar equivalents, and more preferably from about 1.05 to about 1.1 molar equivalents. The mixture is pressurized under hydrogen generally from about 10 to about 500 psi, preferably from about 20 to about 200 psi, and more preferably from about 100 to about 120 psi for about 10 hours, or until the reaction is complete to yield the intermediate compound of formula **IV(i)**. The intermediate compound of formula **IV(i)** need not be isolated and can be used in the next step directly.

Step 3:

To the solution containing the compound of formula **IV(i)** from step 2 is added the compound of formula **Q** (3,4-dialkoxy-3-cyclobutene-1,2-dione), wherein R represents (C₁-C₁₀)alkyl, preferably (C₁-C₆)alkyl, and even more preferably (C₁-C₃)alkyl (e.g., methyl, ethyl, propyl and isopropyl, and preferably ethyl). The compound of formula **Q** can be used generally in at least 1 molar equivalent with respect to the compound of formula **IV(i)**, more preferably from about 1 to about 2 molar equivalents, most preferably from about 1.3 to about 1.5 molar equivalents. The solution is stirred at a temperature ranging from about 0 °C to about 80 °C, preferably from about 20 °C to about 50 °C, more preferably from about 25 °C to about 35 °C, for about 2 hours, or until the reaction is complete to yield the compound of formula **V**. The reaction is preferably catalyzed by a base. Non-limiting examples of suitable bases include KOH, NaOH, Na₂CO₃, K₂CO₃, NaHCO₃, KHCO₃, tetramethylguanidine, DBU, diisopropylethylamine, and the like, or mixtures thereof. Preferred bases include Na₂CO₃, K₂CO₃, or mixtures thereof, more preferably K₂CO₃. To maximize the yield at the end of the reaction, the reaction mixture is acidified with a suitable acid to a pH of about 5 to about 6. Suitable acids include, for example,

carboxylic acids (such as, for example, acetic acid and benzoic acid), and inorganic acids (such as, for example, H_2SO_4 , HCl , and phosphoric acid), with acetic acid being preferred.

5 **Preparation of the compound of formula I**

Method A:

A mixture is prepared containing the compounds of formulae **V** from step 3 and **XI**, a base and a solvent. Non-limiting examples of suitable bases include pyridine, dimethylaminopyridine (DMAP), diisopropylethylamine, $-\text{N}(\text{R}^2)_3$, wherein each R^2 ,
10 which can be the same or different, represents alkyl or cycloalkyl. Preferred bases include $-\text{N}(\text{R}^2)_3$, wherein each R^2 represents alkyl or cycloalkyl, such as, for example, triethylamine, tributylamine and the like. A more preferred base is triethylamine. Suitable solvents include nitrile (such as, for example, acetonitrile), ether (such as, for example, diethylether, THF, dibutylether, and t-butylmethylether), and alcohol
15 solvents (such as, for example, methanol, ethanol, isopropanol, n-propanol, n-butanol, and sec-butanol), more preferably alcohol and nitrile solvents, and even more preferably acetonitrile. The compound of formula **XI** can be added in any molar ratio, preferably in about 1 molar equivalent with respect to the compound of formula **V**, more preferably in about 1.1 molar equivalents. The base can be used generally in at
20 least about 1 molar equivalent with respect to the compound of formula **IV**, preferably from about 1 to about 2 molar equivalents, and more preferably from about 1.3 to about 1.5 molar equivalents. The mixture is heated to a temperature preferably ranging from about 20 °C to about 150 °C, more preferably from about 40 °C to about 80 °C, and even more preferably from about 60 °C to about 70 °C. When the reaction
25 is complete, the reaction mixture is acidified (with, for example, a carboxylic acid, such as, for example, acetic acid and benzoic acid, or an inorganic acid, such as, for example, H_2SO_4 , HCl and phosphoric acid, with acetic acid being preferred) until the pH of the mixture is preferably from about 3 to about 7, more preferably from about 3 to about 5, and even more preferably about 4. The compound of formula **I** can be
30 purified preferably upon crystallization.

Method B:

Step 4(a):

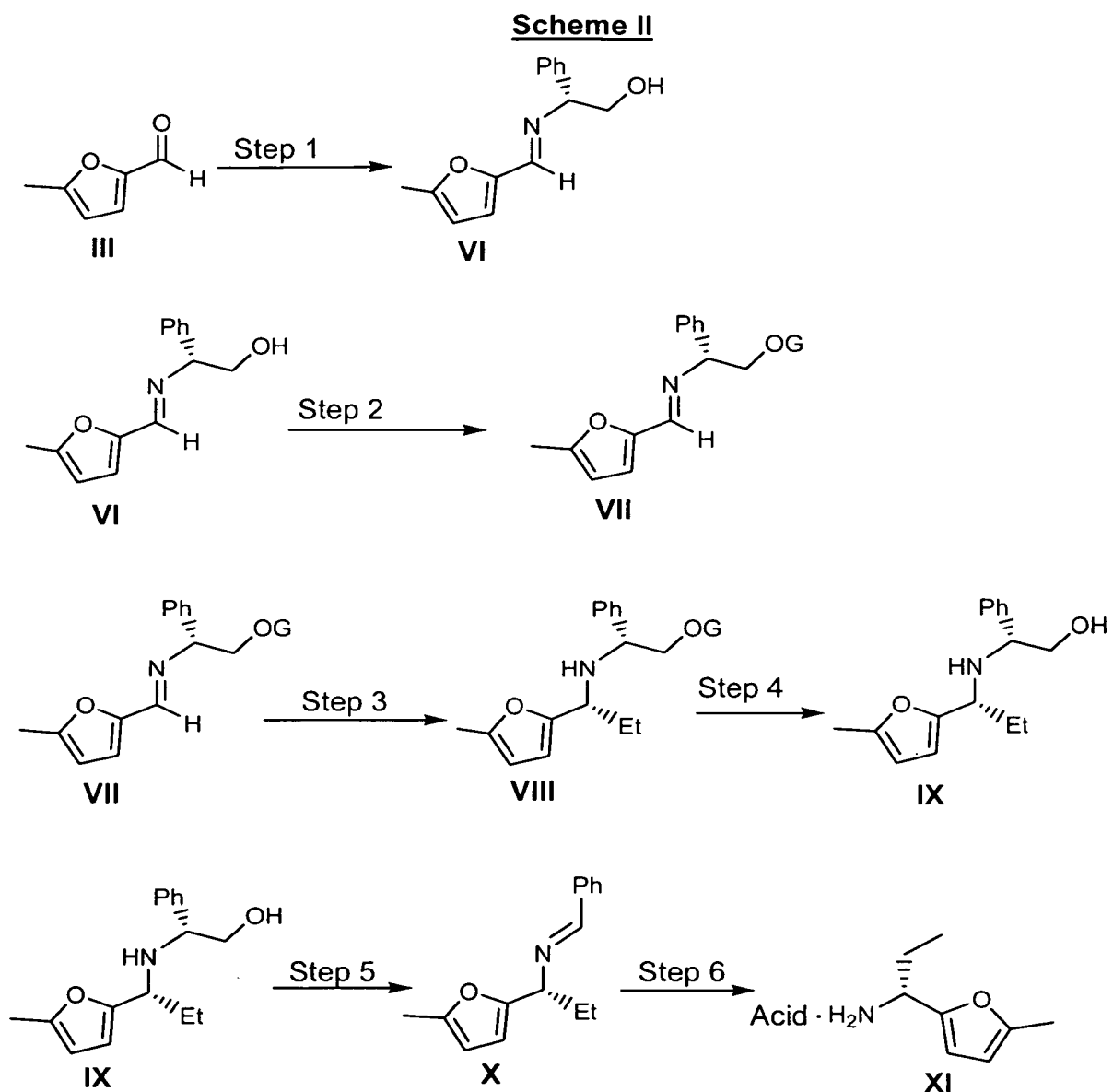
The compound of formula **XI**, is mixed in water and a suitable solvent. Non-limiting examples of suitable solvents include organic solvents such as ethers (such as, for example, diethylether, dibutyl ether and t-butyl methyl ether) and methylene chloride, preferably ethers, more preferably t-butyl methyl ether. The reaction mixture is basified in inorganic base at a temperature ranging preferably from about 0°C to about 50 °C, more preferably from about 10 °C to about 40 °C, and even more preferably from about 20 °C to about 30 °C for about 20 minutes or until the reaction is complete. The reaction mixture is basified to a pH ranging preferably from about 7 to about 14, more preferably from about 10 to about 14, and even more preferably from about 12.5 to about 13.5. Non-limiting examples of suitable bases include inorganic bases such as NaOH, KOH, Mg(OH)₂, Na₂CO₃, K₂CO₃, preferably NaOH and KOH, and even more preferably NaOH. The product of step 4(a) is the free amine compound of formula **XII**.

Step 4(b):

The compound of formula **V** from step 3 is dissolved in a suitable solvent and mixed with the compound of formula **XII** from step 4(a). Non-limiting examples of suitable solvents include alcohol solvents (such as, for example, methanol, ethanol, isopropanol, n-propanol, n-butanol, and sec-butanol), nitrile solvents (such as, for example, acetonitrile), ether solvents (such as, for example, diethylether, THF, dibutylether, and t-butylmethylether), and toluene, more preferably alcohol solvents and nitrile solvents, and more preferably alcohol solvents. The alcohol solvent is preferably n-propanol. A catalytic amount of base is optionally added to the reaction mixture. Suitable bases include organic bases, pyridine or -N(R³)₃ wherein each R³ is independently selected from the group consisting of: alkyl (such as, for example, ethyl, isopropyl, propyl and butyl), aryl (such as, for example, phenyl and tolyl (e.g., p-tolyl)), and aralkyl (such as, for example, benzyl). Preferably, the base is -N(R³)₃. Even more preferably, the base is diisopropylethylamine. The reaction mixture is kept at a temperature ranging preferably from about 10 °C to about 150 °C, more preferably from about 40 °C to about 80 °C, and even more preferably from about 60 °C to about

70 °C, for about 12 hours or until the reaction is complete. The compound of formula **XII** can be added in any molar ratio with respect to the compound of formula **V**, preferably in about 1 molar equivalent with respect to the compound of formula **V**, more preferably in about 1.1 molar equivalents with respect to the compound of formula **V**. The product is the compound of formula **I**, which can be crystallized upon addition of water.

The compound of formula **XI** is prepared following Scheme II:



Step 1:

The compound of formula **III** is mixed with R-2-(-)-phenylglycinol in a suitable solvent. The R-2-(-)-phenylglycinol can be used generally in at least about 0.01 molar equivalent with respect to the compound of formula **III**, preferably from about 0.5 to about 1.5 molar equivalents, more preferably from about 0.9 to about 1.1 molar equivalents. Non-limiting examples of suitable solvents include aromatic solvents such as benzene, toluene, and the like, halogenated solvents such as dichloromethane, methylene chloride, chlorobenzene, and the like, alcohol solvents such as methanol, ethanol, propanol, isopropanol, n-propanol, butanol, and the like, nitrile solvents such as acetonitrile, THF, and the like, ether solvents such as t-butylmethylether, THF, and the like, and mixtures thereof. Preferred solvents include benzene, toluene, THF, dichloromethane, or mixtures thereof, more preferably THF. The solution is heated at reflux for about 2 hours or until the reaction is complete. Step 1 provides the imine compound of Formula **VI**.

Step 2:

The solution containing the compound of Formula **VI** from step 1 is mixed with a silylating reagent and an acid. Suitable silylating reagents include hexamethyldisilazane, TMS chloride, TMSOTF, and the like, wherein the TMS chloride or TMSOTF is used in combination with an aryl or alkyl base. Preferred silylating agents include hexamethyldisilazane, TMS chloride, TMSOTF, wherein the TMS chloride or TMSOTF is used in combination with triethylamine. More preferably, the silylating agent is hexamethyldisilazane. Non-limiting examples of suitable acids include ammonium sulphate, ammonium nitrate, ammonium chloride, H₂SO₄, HCl, H₃PO₄, citric acid, mesyl chloride, paratoluenesulfonic acid, paratoluenesulfonic acid pyridinium salt, alkylsulfonic acid, and the like, or mixtures thereof. Preferred acids include weaker acids such as ammonium sulphate, ammonium nitrate, or ammonium chloride, more preferably ammonium sulphate. The acid can be used generally in at least about 0.2 molar equivalent with respect to the compound of formula **VI**, preferably at least about 0.4 molar equivalents, even more preferably at least about 0.5 molar equivalents. The mixture is heated at reflux for about 2 hours or until the

reaction is complete. The mixture is preferably filtered and concentrated to provide a protected imine compound of Formula VII.

Step 3:

5 The imine compound of Formula VII from step 2 is added to an organometallic reagent in a suitable solvent and then worked up to provide a compound of Formula VIII. The temperature of the reaction can range from about 0 °C to about 80 °C, preferably from about 10 °C to about 50 °C, more preferably from about 20 °C to about 35 °C. Non-limiting examples of suitable organometallic reagents include diethyl zinc, 10 ethylzinc bromide, ethylzinc chloride, ethylmagnesium bromide, ethylmagnesium chloride or ethyllithium, preferably ethylmagnesium bromide or ethylmagnesium chloride, more preferably ethylmagnesium bromide. The organometallic reagent can be used from about 0.1 to about 5 molar equivalents with respect to the compound of formula VII, more preferably from about 1 to about 5 molar equivalents, most 15 preferably from about 2 to about 3 molar equivalents. Non-limiting examples of suitable solvents for the organometallic reagent include benzene, toluene, ether solvents such as TBME or THF, DME, dimethoxyethane, and the like, or mixtures thereof. Preferred solvents include ether solvents such as THF, TBME, and the like, or mixtures thereof, more preferably TBME.

Step 4:

20 The compound of formula VIII from step 3 was slowly added to an aqueous acid cooled to a temperature ranging from about -5 °C to about 20 °C, preferably from about 0 °C to about 15 °C, more preferably from about 0 °C to about 10 °C. 25 Non-limiting examples of suitable acids include H₂SO₄, HCl, H₃PO₄, citric acid, ammonium chloride, and the like, or mixtures thereof. Preferred acids include H₂SO₄, HCl, H₃PO₄, and the like, or mixtures thereof, more preferably H₂SO₄. The amount of acid that can be used can range from about 2.5 to about 5 molar equivalents with respect to the compound of formula VIII, preferably from about 2.5 to about 3 molar 30 equivalents, even more preferably about 2.5 molar equivalents. Water and a co-solvent were then added to the reaction mixture. The co-solvent is preferably an alcohol. Non-limiting examples of suitable co-solvents include methanol, ethanol,

propanol, isopropanol, butanol, sec-butanol, pentanol, hexanol, heptanol, octanol, and the like, or mixtures thereof. Preferred co-solvents include propanol, isopropanol, butanol, sec-butanol, pentanol, hexanol, or mixtures thereof, more preferably sec-butanol. The mixture is stirred for 0.5 hours or until any salts are dissolved. A base is then added to the mixture to adjust the pH of the aqueous phase to obtain the compound of formula IX. The pH of the aqueous phase is preferably adjusted to about 9 to about 13, more preferably to about 10 to about 11, and even more preferably to about 11. Non-limiting examples of suitable bases that can be added include an ammonium hydroxide, metal hydroxide, metal oxide, metal carbonate, metal bicarbonate, and the like, or mixtures thereof, wherein the metal is selected from the group consisting of lithium, sodium, potassium, rubidium, cesium, beryllium, magnesium, calcium, strontium, barium, aluminum, indium, thallium, titanium, zirconium, cobalt, copper, silver, zinc cadmium, mercury and cerium. Non-limiting examples of suitable bases also include bases wherein the base is a metal salt (e.g., Li, Na, K, and Mg, and preferably Na) of a (C₁-C₁₂)alkanol (e.g., methanol, ethanol, propanol, and isopropanol, and preferably methanol), or a (C₃-C₁₂)cycloalkanol (e.g., cyclopentanol, cyclohexanol and cyclooctanol, and preferably cyclohexanol), and the like, or mixtures thereof. Preferred bases include a metal hydroxide, and more preferably KOH, NaOH, NH₄OH, LiOH and CsOH.

Step 5 :

The compound of formula IX from step 4 is dissolved in a suitable solvent (such as, for example, water, methanol, ethanol, propanol, isopropanol, butanol, sec-butanol, pentanol, hexanol, tetrahydrofuran, 1,2-dimethoxyethane, 1,2-diethoxymethane, diglyme, 1,4-dioxane, or mixtures thereof, and preferably ethanol) and cooled to a temperature ranging from about -5 °C to about 20 °C, preferably from about 0 °C to about 15 °C, more preferably from about 0 °C to about 10 °C. To this solution is added R⁴NH₂, wherein R⁴ is selected from the group consisting of alkyl (such as, for example, methyl, ethyl, propyl and butyl), cycloalkyl (such as, for example, cyclohexyl), heterocycloalkyl (such as, for example, piperidinyl and pyrrolidinyl), aryl (such as, for example, phenyl), heteroaryl (such as, for example, pyridyl), and aralkyl (such as, for example benzyl). Thus, examples of R⁴NH₂ include,

for example, methylamine, ethylamine, propylamine, butylamine, 1-(2-aminoethyl)piperidine, 1-(2-aminoethyl)pyrrolidine, cyclohexylamine, aniline, 2-aminopyridine, 3-aminopyridine, 4-aminopyridine, and benzylamine. Preferably, R^4 is (C_1-C_6) alkyl, more preferably (C_1-C_3) alkyl. The addition of R^4NH_2 is followed by the addition of an agent such as $NaIO_4$, $Pb(OAc)_4$, or H_5IO_6 , and the like, or mixtures thereof. The reaction mixture is stirred for about 2 hours or until the reaction is complete to produce the compound of formula **X**.

Step 6:

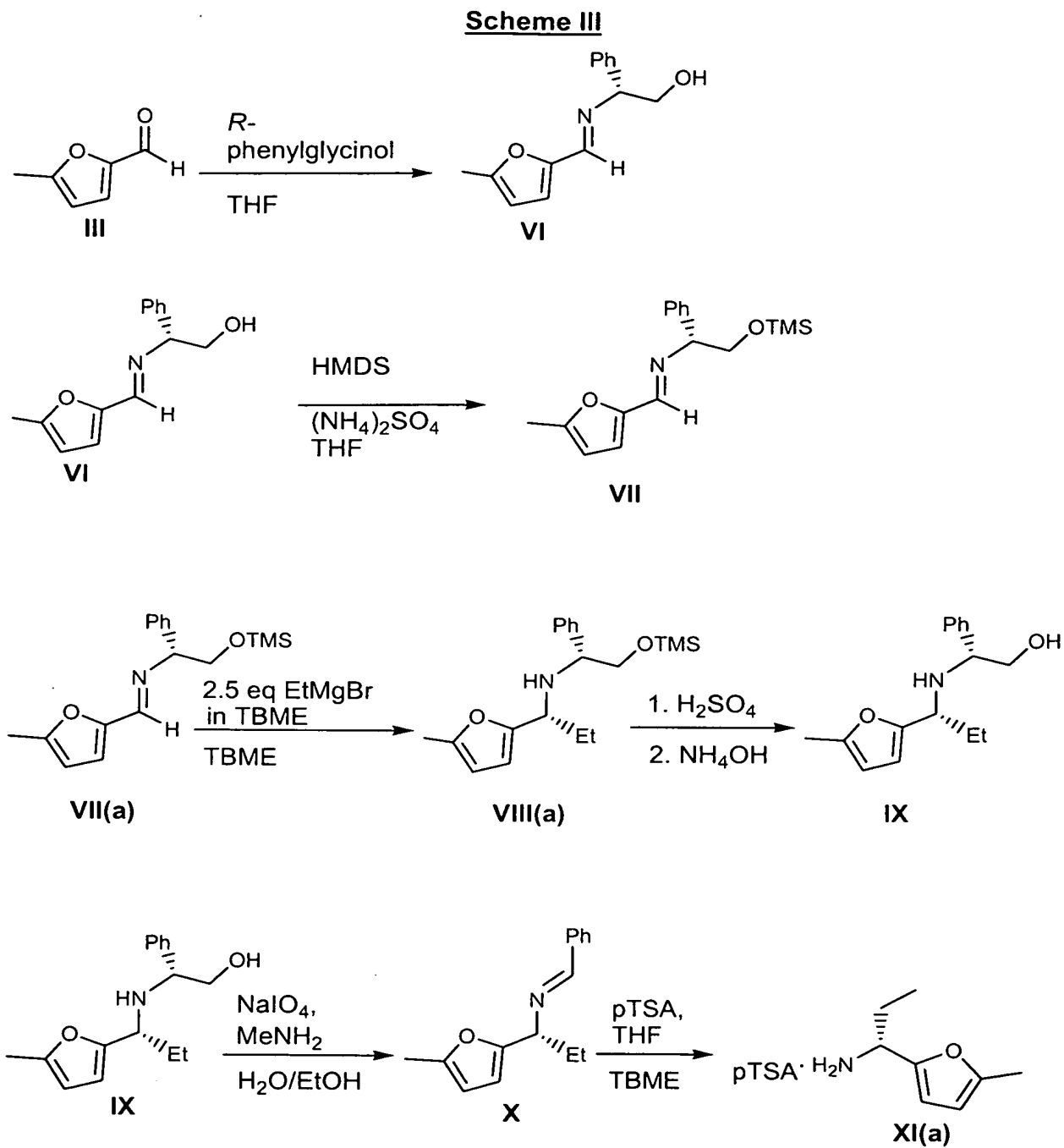
The compound of formula **X** from step 5 is dissolved in 200 mL of a suitable solvent. Non-limiting examples of suitable solvents include hydrocarbon solvents such as toluene, xylene, chlorobenzene, dichlorobenzene, and the like, or ethers such as C_4-C_{12} alkyl ethers (e.g., diethyl ether, dipropyl ether and dibutyl ether), 1,2-dimethoxyethane, 1,2-diethoxyethane, diglyme, 1,4-dioxane, tetrahydrofuran, and the like, or mixtures thereof. This solution is added to a solution of an acid to form a salt at a temperature ranging preferably from about $-50\text{ }^{\circ}\text{C}$ to about $80\text{ }^{\circ}\text{C}$, more preferably from about $-20\text{ }^{\circ}\text{C}$ to about $20\text{ }^{\circ}\text{C}$, even more preferably from about $0\text{ }^{\circ}\text{C}$ to about $10\text{ }^{\circ}\text{C}$. Non-limiting examples of acids include sulfonic acids, tartaric acids, H_2SO_4 , HCl , H_3PO_4 , HBr , carboxylic acids (e.g., acetic acid, benzoic acid and camphoric acid), and the like, and mixtures thereof. Preferred acids are sulfonic acids. Non-limiting examples of sulfonic acids include paratoluene sulfonic acid (pTSA) and alkylsulfonic acids (e.g., methane sulfonic acid and ethane sulfonic acid), with pTSA being preferred. The compound of formula **XI** formed is preferably crystallized from an organic solution.

For the process described in Embodiment No. 2, the compounds of formulas **IV(i)**, **XI**, and **XII** are prepared according to the procedures in Schemes I and II. The compound of formula **XII** is reacted with **Q** to obtain the compound of formula **XIII** using the same reagents and reaction conditions described in Scheme I to react the compound of formula **V** with the compound of formula **XII**. Then the compound of formula **IV(i)** is reacted with the compound of formula **XIII** to obtain the compound of formula **I** using the same reagents and reaction conditions described in Scheme I to react the compound of formula **IV(i)** with the compound of formula **Q**.

The following nonlimiting examples are provided in order to further illustrate the present invention. It will be apparent to those skilled in the art that many modifications, variations and alterations to the present disclosure, both to materials, methods and reaction conditions, may be practiced. All such modifications, variations and alterations are intended to be within the spirit and scope of the present invention.

Preparative Example 1: Preparation of Compound XI(a)

The compound of formula **XI(a)** was prepared following Scheme III:



Step 1. Preparation of the compound of Formula VI:

To a 2-L 3-necked round-bottomed flask equipped with Dean-Stark apparatus was added R-2-(-)-phenylglycinol (124.6 g, 908 mmol) and 1000 mL of THF. To this solution was added 5-methylfurfural **III** (100 g, 908 mmol) (Bedoukian Research, 21 Finance Drive, Danbury, CT 06810). This solution was heated at reflux with azeotropic removal of water for 2 hours. Concentration of the solution provided imine of Formula **VI**. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.04 (s, 1H), 7.44-7.25 (m, 5H), 6.68 (d, J = 3.3 Hz, 1H), 6.09 (dd, J = 3.3, 0.8 Hz, 1H), 4.42 (dd, J = 8.9, 4.2 Hz, 1H), 4.08 (dd, J = 8.9, 4.2 Hz, 1H), 3.91 (dd, J = 11.4, 4.2 Hz, 1H), 3.12 (br, s, 1H), 2.39 (s, 3H). ¹³C NMR (100.62 MHz, CDCl₃) δ (ppm) 156.2, 151.8, 150.2, 140.9, 128.9, 127.9, 127.8, 117.5, 108.7, 77.8, 67.9, 14.4.

Step 2. Preparation of the compound of Formula VII(a):

The solution of Formula **VI** was added to ammonium sulphate (12 g, 91 mmol). Hexamethyldisilazane (73.3 g, 454 mmol) was added over 0.5 hour. The mixture was heated at reflux for 2 hours. The mixture was filtered and concentrated to an oil to provide TMS protected imine of Formula **VII(a)**. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.01 (s, 1H), 7.43-7.18 (m, 5H), 6.60 (d, J = 3.3 Hz, 1H), 6.01 (dd, J = 3.3, 0.9 Hz, 1H), 4.29 (dd, J = 7.3, 5.8 Hz, 1H), 3.88 (br, unresolved d, 1H), 3.86 (d, J = 2.4 Hz, 2H), 2.32 (s, 3H), 0 (s, 9H). ¹³C NMR (100.62 MHz, CDCl₃) δ (ppm) 155.9, 151.7, 150.6, 141, 128.7, 127.9, 127.6, 116.9, 108.5, 77.3, 68.0, 14.4, 2.4, 0.

Step 3. Preparation of the compound of Formula VIII(a):

To a 5 L 3-necked round bottomed flask containing EtMgBr 1 M in TBME (2270.5 mL, 2.27 mol) at 20 °C was added imine of Formula **VII(a)** while maintaining the temperature below 35 °C. After addition was completed, an aliquot was removed and quenched into a saturated solution of ammonium chloride, extracted with TBME, and concentrated to an oil to provide an imine of Formula **VIII(a)**. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.23-7.09 (m, 5H), 5.81 (d, J = 3 Hz, 1H), 5.67 (dd, J = 3, 1 Hz, 1H), 3.77 (dd, J = 8.1, 4.6 Hz, 1H), 3.56 (dd, J = 10.1, 4.6 Hz, 1H), 3.5 (br, unresolved dd, 2H), 2.11 (s, 3H), 1.73 – 1.62 (m, 2H), 0.74 (t, J = 7.4 Hz, 3H), 0 (s, 9H).

Step 4. Preparation of the compound of Formula IX:

A solution of the amine compound of Formula VIII(a) was slowly added over 1 hour to 1000 mL of 2.5M sulfuric acid cooled to 10°C. After addition was completed, 500 mL of sec-butanol and 500 mL of water was added and the mixture was stirred
5 for 0.5 hours to dissolve any salts formed. The mixture was then transferred to a separatory funnel and the bottom aqueous layer separated. To the top organic phase was added 250 mL of 25% ammonium hydroxide until the pH of the aqueous phase was 11. The bottom aqueous phase was separated and the organic phase washed twice with 500 mL of 5 % brine solution. The organic phase was then treated with 20
10 g of Darco and 20 g of celite and filtered. The organic phase was concentrated to an oil to provide an amine compound of Formula IX. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.22-7.12 (m, 5H), 5.84 (d, J = 2.99 Hz, 1H), 5.69 (dd, J = 2.99, 1 Hz, 1H), 3.72 (dd, J = 7.3, 4.6 Hz, 1H), 3.62 (dd, J = 10.8, 4.6 Hz, 1H), 3.49-3.43 (m, 2H), 2.07 (s, 3H), 1.73-1.62 (m, 2H), 0.77 (t, J = 7.4 Hz, 3H). ¹³C NMR (100.62 MHz, CDCl₃) δ (ppm)
15
154.9, 151.4, 141.8, 128.9, 127.8, 127.7, 107.8, 106.1, 66.4, 62.3, 56.4, 27.6, 14, 11.1.

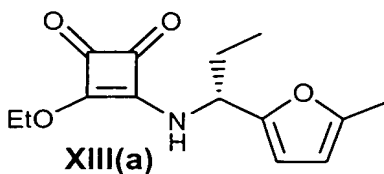
Step 5. Preparation of the compound of Formula X:

The amine of Formula IX was dissolved in 500 mL EtOH and cooled to 0 °C.
20 To this solution was added MeNH₂ (40% by wt. In H₂O) (80 mL, 928 mmol) followed by addition of a solution of NaIO₄ (200 g, 934 mmol) dissolved in 1000 mL H₂O. After stirring 2 hours at room temperature, the reaction is filtered and the inorganic solids rinsed with 600 mL methy t-butyl ether (TBME). The filtrate was separated and the organic phase washed with 1000 mL H₂O and then with 1000 mL of 5 % NaCl
25 solution. After concentration of the organic phase an oil was obtained of intermediate of Formula X. The oil is dissolved in 200 mL THF. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.17 (s, 1H), 7.64-7.62 (m, 2H), 7.27-7.24 (m, 3H), 5.96 (d, J = 3 Hz, 1H), 5.75 (dd, J = 3, 0.9 Hz, 1H), 4.09 (dd, J = 8.1, 5.8 Hz, 1H), 2.11 (s, 3H), 1.97-1.78 (m, 2H), 0.79 (t, J = 7.4 Hz, 3H).

Step 6. Preparation of the compound of Formula XI(a):

The solution containing the compound of formula **X** from step 5 was added to a solution of p-toluene sulfonic acid (160 g, 840 mmol) dissolved in 400 mL THF at 0 °C. This solution was stirred at 25 °C for 1-4 hours and then diluted with 600 mL TBME. After stirring at 25 °C for 6-14 hours, the heterogeneous reaction mixture was filtered and the solids were washed with 800 mL 3:1 TBME/THF and dried in a vacuum oven at 40 °C for 6 hrs to provide the compound of formula **XI(a)** 75-80 % yield. The compound of formula **XI(a)** was used to prepare the compound of formula **I** as described earlier. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.09 (br s, 3H), 7.68 (d, J = 7.4 Hz, 2H), 7.15 (d, J = 7.6 Hz, 2H), 6.22 (d, J = 3.2 Hz, 1H), 5.82 (dd, J = 3.1, 1 Hz, 1H), 4.05 (dd, J = 8, 6.5 Hz, 1H), 2.38 (s, 3H), 2.14 (s, 3H), 1.9-1.83 (m, 2H), 0.74 (t, J = 7.4 Hz, 3H). ¹³C NMR (100.62 MHz, DMSO-d₆) δ 152.2, 148.3, 145.6, 137.8, 128.1, 125.5, 110.2, 106.8, 47.9, 24.9, 20.8, 13.3, 9.9. Mp 117 °C. HRMS calcd for C₈H₁₄NO (FAB+ m/z M+H) 140.1075, found 140.1072. Anal. calcd. for C₁₅H₂₁NO₄S: C: 57.86; H: 6.80; N: 4.50. Found: C: 57.90; H: 6.93; N: 4.26.

Preparative Example 2: Preparation of Compound XIII(a)



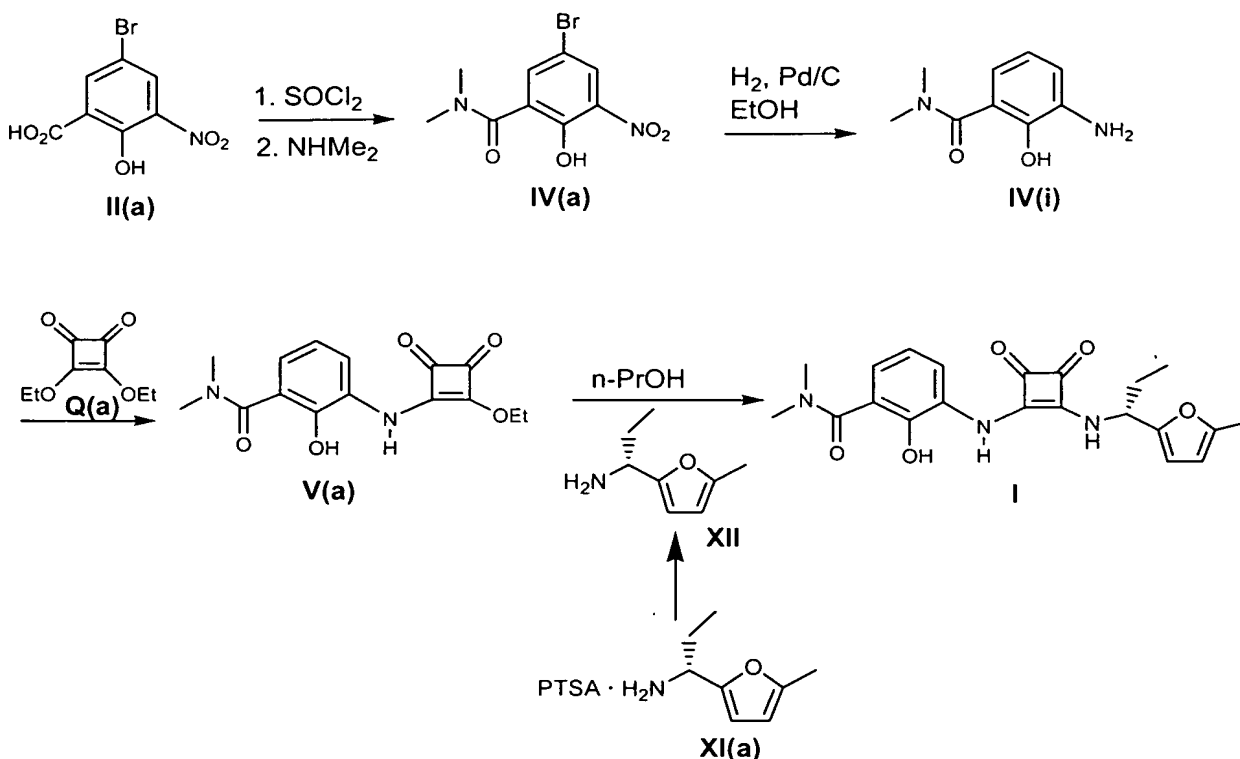
To a mixture containing 3,4-diethoxyl-3-cyclobutene-1,2-dione (diethyl squarate, 2.53 g, 14.88 mmol, 1.05 eq), and compound **XI(a)** (4.41g, 14.16 mmol, 1.0 eq) in ethanol (27 ml) was charged triethylamine (2 ml, 14.23 mmol, 1.0 eq). The batch was stirred at ambient temperature for 3 hours, filtered through a silica gel pad, washed with ethanol and concentrated. The resulting oil was purified via column chromatography to afford compound **XIII(a)**, thick colorless oil, in 97.2% yield (3.625 g). ¹H NMR (400MHz, DMSO-d₆) δ (ppm) 9.16 (br d, 0.5H), 8.97 (br d, 0.5H), 6.17 (s, 1H), 6.01 (s, 1H), 5.02 (br m, 0.5H), 4.67 (m, 2H), 4.54 (br m, 0.5H), 2.22 (s, 3H), 1.92 (m, 0.5H), 1.82 (m, 0.5H), 1.37 (t, J=7.0Hz, 3H), 0.90 (t, J=7.3Hz, 3H). ¹³C NMR (DMSO-d₆) δ (ppm) 189.14, 188.94; 182.41, 182.09; 177.11, 176.62; 172.42, 171.76;

152.45, 152.01; 151.15; 107.34; 106.38; 68.91; 53.92, 52.99; 26.08, 25.90; 15.59; 13.22; 10.44. FAB+ m/z 264.2 (M+H).

Example 1

The compound of formula I was prepared following Scheme IV:

Scheme IV



Step 1: Preparation of 2-Hydroxy-N,N-dimethylbenzamide (IVa)

To a three neck flask was charged (50.0 g, 190.8 mmol) of 5-bromo-3-nitrosalicylic acid (Davos, 464 Hudson Terrace, Englewood, NJ 07362), 200 ml of acetonitrile and 14 ml (191.9 mmol) of thionyl chloride. The resulting mixture was heated at 70°C for 2 hours. The mixture was then cooled to 5-10°C and a solution of dimethylamine in THF (2M, 210ml, 2.2 eq.) was added slowly over one hour. The reaction mixture was then warmed to ambient temperature and stirred for another 3 hours. The mixture was mixed with 100 ml of water and acidified with sulfuric acid

(2N, 45ml) to a pH of 2. Additional 800 ml of water was added slowly over one hour while solids product precipitated out from the mixture. The suspension was cooled to 5 °C. The solids were filtered and washed with water (200ml). The wet crude product was recrystallized from 400 ml of hot ethanol to give 44.2 g (80%) of the compound of formula **IV(a)**. Melting point: 181 °C -183 °C. ¹H NMR (400MHz, DMSO): δ (ppm) 10.94 (s, 1H), 8.16 (d, 1H, *J*=2.5Hz), 7.76 (d, 1H, *J*=2.5Hz), 2.9 (br, 6H). ¹³C NMR (100.62 MHz, DMSO): 164.7, 147.5, 137.6, 135.9, 131.5, 127.4, 110.0, 37.6, 34.3. Anal. calcd. for C₉H₉BrN₂O₄ (289.08): C, 37.39; H, 3.14; N, 9.69. Found: C, 37.42; H, 2.90; N, 9.55.

Step 2: Preparation of 5-bromo-2-hydroxy-3-nitro-N,N-dimethylbenzamide (Va)

A mixture of 25.0 g (86.5 mmol) of compound **IV(a)**, 5.5 g of 5% Pd/C (50 % water), 12.3 g (88.8 mmol) of potassium carbonate and 200 ml of ethanol was pressurized under hydrogen at 105 psi with agitation at room temperature for 10 hours. The reaction mixture was analyzed by ¹H NMR (400MHz, CDCl₃): δ (ppm) 2.9 (s, 6H), 3.9 (br, 2H), 6.47(q, 1H), 6.55(m, 2H). If the conversion of compound **IV(a)** to intermediate **IV(i)** was found not complete, additional 0.5 g of Pd/C catalyst was charged and the mixture was kept under hydrogen pressure at 105 psi for 5 more hours. The mixture was then filtered through a Celite bed and the cake was washed with 30 ml of ethanol. Caution should be taken to ensure minimum exposure of the product solution to air during the filtration. The filtrate was immediately transferred into one-liter three neck flask fitted with a reflux condenser, mechanic stirrer, and nitrogen inlet. The solution was cooled to 5 °C and a solution of 19.9 g (116.7 mmol, 1.35 eq.) of 3,4-diethoxy-3-cyclobutene-1,2-dione (diethyl squarate) (Compound of formula **Q(a)**) (Lonza, Inc. Corporate Headquarters, 17-17 Route 208, Fair Lawn, NJ 07410) in 80 ml ethanol was added in one portion. The solution was slowly warmed up to 25 °C in 2 hours. If there were no product solids precipitating from the reaction mixture, a small amount (~100 mg) of potassium carbonate was added. The suspension was stirred for another 5 hours at room temperature. The mixture was then slowly heated to reflux over 1 hour before it was slowly cooled to 10 °C over 2 hours. During the heating, a small amount of compound **IV(i)** trapped inside the product solids was released and converted to the product **V(a)**. The solids were collected by filtration

and the cake was washed with 40 ml of cool ethanol. The solids were dried in a vacuum oven at 60 °C for 5 hours to give 21.3 g (80.9%) of the compound of formula **V(a)**. ¹H NMR (400MHz, CD₃CN): δ (ppm) 1.4(t, 3H), 3.1(s, 6H), 4.8 (q,2H), 6.9 (dd,3H), 7.2(d,1H), 7.6 (d,1H), 8.1(br, 1H), 10.5 (br,1H). Mp: 180-183 °C. ¹³C NMR (100.62 MHz, DMSO): 188.2, 184.1, 178.0, 171.3, 167.9, 146.9, 125.9, 125.8, 125.7, 125.6, 119.3, 68.1, 37.6, 34.6, 15.6. Anal. calcd. for C₁₅H₁₆N₂O₅ (304.30): C, 59.21; H, 5.30; N, 9.21. Found: C, 59.12; H, 5.29; N, 9.14.

Step 3: Preparation of 2-Hydroxy-N,N-dimethyl-3-[[2-[[1(R)-(5-methyl-2-furanyl)propyl]amino]-3,4-dioxo-1-cyclobuten-1-yl]amino]benzamide (compound I)

Method A:

A mixture containing 10.0 g (32.9 mmol) of compound **V(a)**, 11.1 g (35.6 mmol, 1.08eq.) of compound **XI(a)** from Scheme III, 6.2 ml (44.4 mmol, 1.35eq.) of triethylamine and 120 ml of acetonitrile was heated at 65 °C with agitation for 4 hours. The mixture was then cooled to 50 °C and 2.0 g of charcoal was added. The resulting suspension was heated at 70 °C for 1 hour. The reaction mixture was cooled to 40 °C and filtered through a Celite bed. The Celite cake was washed with 30 ml of acetonitrile. The filtrate was charged back to a three neck flask and about 12 ml of 1N sulfuric acid was added slowly until the pH of the mixture was about 4. Water (180 ml) was added slowly at 50 °C over one hour and the resulting suspension was cooled to 15 °C over 1 hour. The solids were collected by filtration and the cake was washed with 50 ml of water. The ¹H NMR of the wet cake showed that the product was contaminated by about 15% p-toluenesulfonic acid. The wet cake was charged back to a three neck flask along with 130 ml of acetonitrile. The mixture was heated to 70 °C to dissolve all solids. Water (150 ml) was added slowly over half an hour at 55 °C with good agitation. The resulting suspension was cooled to 10 °C over one hour. The solids were collected by filtration and the cake was washed with 40 ml of water. The product was dried in a vacuum oven over night at 60 °C, to give 10.6 g (77.6%) of the title compound I, Mp: 83 °C. ¹H NMR (400 MHz, DMSO): δ (ppm) 1.0 (t,3H), 1.9 (m, 1H), 2.0 (m,1H), 2.3 (s,3H), 3.0 (S, 6H), 5.2 (dd,1H), 6.1(d,1H), 6.3 (d,

1H), 6.9 (m, 2H), 7.8 (d, 1H), 8.7 (d, 1H), 9.3 (dr, 1H), 10.0 (br, 1H). ¹³CNMR(100.62, CD₃CN): 185.2, 182.0, 171.8, 170.1, 164.6, 153.4, 153.0, 148.9, 129.2, 124.1, 122.9, 119.4, 119.0, 108.4, 107.2, 54.8, 38.7, 28.3, 13.5, 10.6.

5 **Method B:**

To a three neck round bottom flask were charged 41.2 g (132.4 mmol) of compound **XI(a)**, 200 ml of water and 100 ml of t-butyl methylether. The solution was agitated and a 25% sodium hydroxide solution (18 ml) was added slowly over 20 min while maintaining the temperature of the reaction mixture below 30 °C. The resulting solution was transferred into a separation funnel and the aqueous was extracted another two times with 100 ml of t-butyl methylether. The combined organic was washed with 100 ml of saturated sodium chloride solution. The solvent was removed under vacuum and the residue containing free amine **XII** was dissolved in 360 ml of n-propanol. The resulting solution was mixed with 40.0 g (128.5 mmol) of compound **V(a)** and 0.4 g (3.1 mmol, 0.024 eq.) of diisopropylethylamine. The mixture was heated at 65 °C for 12 hours. Another 120 ml of n-propanol and 400 ml of water was charged. The mixture was then heated up to about 70 °C and slowly cooled to 10 °C. The solids were collected by filtration and washed with 80 ml of aqueous solution containing 50% of n-propanol. The resulting wet cake was dried in a vacuum oven at 60 °C over night, to give 44.7 g (81.9%) of the compound of formula I.

For the process described in Embodiment No. 2, the compounds of formulas **IV(i)**, **XI(a)**, and **XII** are prepared according to the procedures in Schemes III and IV. The compound of formula **XII** is reacted with **Q** to obtain the compound of formula **XIII** using the same reagents and reaction conditions described in Scheme I to react the compound of formula **V** with the compound of formula **XII**. Then the compound of formula **IV(i)** is reacted with the compound of formula **XIII** to obtain the compound of formula I using the same reagents and reaction conditions described in Scheme I to react the compound of formula **IV(i)** with the compound of formula **Q**.

EXAMPLE 2

To a solution of 0.58 g (2.20 mmol) of compound **XIII(a)** in 25 ml ethanol were added 20 mg potassium carbonate (~0.02 eq.) and a solution of 3 mmol of active compound of formula **IV(i)** (1.36 eq) in 10 ml of ethanol. The resulting mixture was
5 heated at 60°C for about 3.5 hours. Upon completion of the reaction, compound **I** was isolated via the same procedure as the method B, in similar yield (83% by assay).

It will be understood that various modifications can be made to the embodiments and examples disclosed herein. Therefore, the above description
10 should not be construed as limiting, but merely as exemplifications of preferred embodiments. Those skilled in the art will envision various modifications within the scope and spirit of the claims appended hereto.